PTO/SB/17 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995 no persons are required to respond to a collection of information unless it displays a valid OMB control number

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2007

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($)

Complete if Known	
Application Number	6,884, 434
Filing Date	Issued Date: 26 April 2005
First Named Inventor	Walter Mueller
Examiner Name	TBA
Art Unit	N/A
Attorney Docket No.	6102-500097

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☑ Deposit Account Deposit Account Number: 08-0750 Deposit Account Name: Harness Dickey & Pierce

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☑ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☑ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☐ Credit any overpayments

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

Application Type	FILING FEES Fee ($)	FILING FEES Small Entity Fee ($)	SEARCH FEES Fee ($)	SEARCH FEES Small Entity Fee ($)	EXAMINATION FEES Fee ($)	EXAMINATION FEES Small Entity Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

RECEIVED
JUL 6 2007
OPLA

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____ - 20 or HP =	_____ x	_____ =	_____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____ - 3 or HP =	_____ x	_____ =	_____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims: Fee ($) _____ Fee Paid ($) _____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
_____ - 100 =	_____ / 50 =	_____ (round up to a whole number) x	_____ =	_____

4. OTHER FEE(S)

Fees Paid ($)

Non-English Specification, $130 fee (no small entity discount)

Other (e.g., late filing surcharge): Application for Extension of Patent Term

09/20/2007 TDEY11 00000001 080750 6884434
Sale Ref: 00000001 DAN: 080750 6884434
01 FC:1457 1120.00 DA

SUBMITTED BY

Signature	J. Timothy Keane	Registration No. (Attorney/Agent) 27, 808	Telephone 314-726-7500
Name (Print/Type)	J. Timothy Keane		Date 06 July 2007

This collection of information is required by 37 CFR 1.136. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 6,884,434

Title: TRANSDERMAL THERAPEUTIC SYSTEM WHICH CONTAINS A D2 AGAONIST AND WHICH IS PROVIDED FOR TREATING PARKINSONISM, AND A METHOD FOR THE PRODUCTION THEREOF

Issue Date: 26 April 2005

Inventors: Walter Muller and James V. Peck

Assignee and Owner: LTS Lohmann Therapie-Systeme AG and Schwarz Pharma Limited

Licensee and Agent: Schwarz Pharma Limited

Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984 (35 U.S.C. §156), Schwarz Pharma Limited, requests an extension of the patent term of U.S. Patent No. 6,884,434. The relevant facts establishing the authority of Schwarz Pharma Limited to file this Application for Extension of Patent Term in accordance with 37 C.F.R. 1.730 are set forth below:

- Schwarz Pharma AG received a license under U.S. Patent No. 6,884,434 from Aderis Pharamceuticals, Inc. (formerly Discovery Therapeutics, Inc.) effective 17 July 1998. This license was assigned to Schwarz Pharma Limited on 30 December 2002.

- Schwarz Pharma AG received a license under U.S. Patent No. 6,884,434 from LTS Lohmann Therapie-Systeme AG, effective 25 January 1999. This license was assigned to Schwarz Pharma Limited on 30 December 2002.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 6,884,434

Title: TRANSDERMAL THERAPEUTIC SYSTEM WHICH CONTAINS A D2 AGAONIST AND WHICH IS PROVIDED FOR TREATING PARKINSONISM, AND A METHOD FOR THE PRODUCTION THEREOF

Issue Date: 26 April 2005

Inventors: Walter Muller and James V. Peck

Assignee and Owner: LTS Lohmann Therapie-Systeme AG and Schwarz Pharma Limited

Licensee and Agent: Schwarz Pharma Limited

July 6, 2007
TRANSMITTAL LETTER

Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

ATTN: Mary Till, Esq.

Dear Ms. Till:

In support of the Application for Patent Term Extension of U.S. Patent No. 6,884,434, Applicants submit the following:

1. PTE Application (being submitted as one original and two additional copies thereof)
2. Exhibits A-O
3. Duplicate Fee Transmittal Sheet

Applicant certifies that the two additional copies are identical to the original being submitted.

RECEIVED
JUL 6 2007
OPLA

Respectfully submitted,

J. Timothy Keane
Registration No. 27,808

Enclosures
cc: Dr. Sabine Krohn

- Schwarz Pharma AG, through Schwarz BioSciences, Inc., is the holder of the regulatory approval granted for the NEUPRO® transdermal system for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease.

- On 04 October 2000 and 20 November 2000, Walter Muller and James V. Peck (the inventors of the subject matter claimed in the U.S. Patent No. 6,884,434) assigned to LTS Lohmann Therapie-Systeme AG and Discovery Therapeutics, Inc. all rights in Serial No. 09/647,290 (issued as U.S. 6,884,434). This assignment was recorded in the United States Patent and Trademark Office on 28 November 2000 at Reel 011139, Frame 0596. A copy of this assignment is attached as Exhibit A.

- On 04 January 2002, Discovery Therapeutics, Inc. changed its name to Aderis Pharmaceuticals, Inc. This name change was recorded in the United States Patent and Trademark Office on 23 July 2002 at Reel 013107, Frame 0011. A copy of this name change is attached as Exhibit B.

- On 14 July 2005, Aderis Pharmaceuticals, Inc. assigned to Schwarz Pharma Limited all rights in U.S. Patent No. 6,884,434. This assignment was recorded in the United States Patent and Trademark Office on 20 July 2005 at Reel 016283, Frame 0716. A copy of this assignment is attached as Exhibit C.

- LTS Lohmann AG has executed a power of attorney in favor of Schwarz Pharma AG (parent of Schwarz Pharma Limited), authorizing the filing of the present Application for Extension of Patent Term of behalf of LTS Lohmann AG. A copy of this power of attorney is attached as Exhibit D.

- LTS Lohmann Therapie-Systeme AG and Schwarz Pharma Limited have each executed a power of attorney in favor of Harness, Dickey, & Pierce, PLC. Copies of these powers of attorney are attached as Exhibit D.

The following information is submitted in accordance with 35 U.S.C. §156(d) and 37 C.F.R. 1.740 to 1.741. For convenience, the formal requirements of 37 C.F.R. 1.740 are specifically set out below and underlined in accordance with the numerical format set forth therein.

(a) An application for extension of patent term must be made in writing to the Director. A formal application for the extension of patent term must include:

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics;

The approved product is NEUPRO® (rotigotine) 2 mg/24 hr., 4 mg/24 hr., and 6 mg/24 hr. transdermal systems. Rotigotine is the active ingredient in the NEUPRO® (rotigotine) transdermal systems. Rotigotine is further identified as follows:

The chemical name for rotigotine is (6S)-6-{propyl[2-(2-thienyl)ethyl]amino}-5,6,7,8-tetrahydro-1-naphthalenol. The CAS registry number for rotigotine is 99755-59-6.

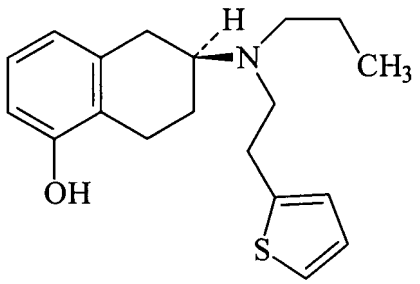
U.S. Patent No. 6,884,434 identifies rotigotine by the alternative name of (–)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl-ethyl]amino-1-naphthalenol.

The generic name of the active ingredient in NEUPRO® (rotigotine) transdermal systems is rotigotine. Rotigotine is the U.S. Adopted Name (USAN) and International Nonproprietary Name (INN) for this compound.

The molecular formula of rotigotine is $C_{19}H_{25}NOS$.

The molecular weight of rotigotine is 315.48.

The structural formula of rotigotine is:



Rotigotine is the active ingredient in the approved product, NEUPRO® (rotigotine) transdermal systems, as illustrated in the approved package insert and patient package insert attached as Exhibit E. As illustrated in Exhibit E, the NEUPRO® (rotigotine) transdermal systems are composed of three layers: (1) backing film; (2) drug matrix; and (3) protective liner. The drug matrix layer contains the following inactive ingredients: ascorbyl palmitate, povidone, silicone adhesive, sodium metabisulfite, and dl-alpha-tocopherol.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

The approved product, the NEUPRO® (rotigotine) transdermal systems, were subject to regulatory review under Section 505(b) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. §355(b), as amended.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.

The NEUPRO® (rotigotine) transdermal systems were approved by the Food and Drug Administration ("FDA") for commercial marketing pursuant to Section 505(b) of the FFDCA on 09 May 2007. A copy of the letter from the FDA, dated 09 May 2007, setting forth the approval of the product is attached as Exhibit F.

(4) **In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing of use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.**

The only active ingredient in the NEUPRO(R) transdermal systems is rotigotine, which has not been approved previously for commercial marketing or use under the FFDCA, the Public Health Service Act, the Virus-Serum-Toxin Act, or any other federal statute.

(5) **A statement that the application is being submitted within the sixty day period permitted for submission pursuant to §1.720(f), and an identification of the date of the last day on which the application could be submitted.**

The present Application for Extension of Patent Term is being submitted within the sixty-day period permitted for submission under 37 C.F.R. 1.720(f). The FDA approved the commercial marketing and use of the approved product, NEUPRO(R) (rotigotine) transdermal systems on 09 May 2007. The sixty-day submission period ends on July 7, 2007, however, because the deadline falls on a Saturday, the present application for extension of patent term can be timely submitted on Monday, July 9, 2007. As demonstrated by the signed Certificate of Hand-Delivery, this application for Extension of Patent Term is timely submitted.

(6) **A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.**

U.S. Patent No.:	6,884,434
Title:	TRANSDERMAL THERAPEUTIC SYSTEM WHICH CONTAINS A D2 AGONIST AND WHICH IS PROVIDED FOR TREATING PARKINSONISM, AND A METHOD FOR THE PRODUCTION THEREOF
Issue Date:	26 April 2005
Expiration Date:	18 March 2019
Application No.:	09/647,290
Application Filing Date:	18 March 1999 (35 U.S.C. §371 Date: 28 November 2000)
Inventors:	Walter Muller and James V. Peck
Assignee and Owner:	LTS Lohmann Therapie-Systeme AG and Schwarz Pharma Limited
Licensee and Agent:	Schwarz Pharma Limited

(7) **A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.**

A copy of U.S. Patent No. 6,884,434, the patent for which extension is being requested, is attached as Exhibit G. This copy contains the entire specification (including claims) for U.S. Patent No. 6,884,434. There is one drawing in the U.S. Patent No. 6,884,434.

(8) **A copy of any disclaimer, certificate of correction, receipt for maintenance fee payment, or reexamination certificate issued in the patent.**

No disclaimer, certificate of correction or reexamination certificate has issued for U.S Patent No. 6,884,434.

(9) **A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claims read on.**

U.S. Patent No. 6,884,434 claims a transdermal therapeutic system. Each applicable patent claim is set forth below together with a showing of the manner in which each applicable patent claim reads on the approved product.

Following is a detailed explanation of how Claims 1, 5, 7, and 14-15 read on the approved product.

Exhibit H provides a summary of the NEUPRO® transdermal system components, redacted from a complete list of the amounts and components provided in the 19 January 2005 NDA submission.

Exhibit E provides the package insert and patient package insert as provided in the 09 May 2007 approval letter.

> *Claim 1. A transdermal therapeutic system comprising a self-adhesive matrix layer containing the free base (−)-5,6,7,8-tetrahydro-6-[propyl-1[2-(2-thienyl)ethyl]amino]-1-naphthalenol in an amount effective for the treatment of the symptoms of Parkinson's syndrome, wherein the matrix is based on a an acrylate-based or silicone-based polymer adhesive system having a solubility of ≥5% (w/w) for the free base (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol, all of said free base being present in the matrix in the absence of water; a backing layer inert to the components of the matrix layer; and a protective foil or sheet covering the matrix layer to be removed prior to use.*

NEUPRO® transdermal system: The 09 May 2007 NDA approval as provided in Exhibit F states that the NEUPRO® transdermal systems contain rotigotine free base and are approved for treating the symptoms of early-stage idiopathic Parkinson's disease. As illustrated in Exhibit H, the matrix is composed of silicone pressure-sensitive adhesives and rotigotine is dispersed in this matrix. As further illustrated in Exhibit H, the NEUPRO® transdermal systems contain ≥5% (w/w) rotigotine free base. As illustrated in Exhibit H, purified water used during the manufacture of the transdermal system is not present in the finished product. As illustrated in Exhibit E, the NEUPRO® transdermal systems contain a flexible, tan-colored backing film,

consisting of an aluminized polyester film coated with a pigment-layer on the outer side. As further illustrated in Exhibit E, the NEUPRO® transdermal systems contain a protective liner, consisting of a transparent fluoropolymer-coated polyester film . . . removed just prior to application.

Claim 5. The transdermal therapeutic system of claim 1 wherein the silicone-based polymer adhesive in the matrix layer further comprises additives to enhance the solubility of (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol in the form of hydrophilic polymers or glycerol or glycerol derivatives.

NEUPRO® transdermal systems: As illustrated in Exhibits E and H, the NEUPRO® transdermal systems comprise the hydrophilic polymer povidone.

Claim 7. The transdermal therapeutic system of claim 5 wherein the silicone-based polymer adhesive contains between 5 to 25% (w/w) (−)-5,6,7,8-tetrahydro[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol.

NEUPRO® transdermal systems: As illustrated in Exhibit H, the NEUPRO® transdermal systems contain between 5 to 25% (w/w) rotigotine free base.

Claim 14. The transdermal therapeutic system of claim 5, wherein the hydrophilic polymer is selected from the group of polyvinylpyrrolidone, a copolymer of vinylpyrrolidone and vinylacetate, polyethyleneglycol, polypropylene glycol, and a copolymer of ethylene and vinylacetate.

NEUPRO® transdermal systems: As illustrated in Exhibit E, the NEUPRO® transdermal systems contain povidone. As provided in Exhibit I, povidone is synonymous with polyvinylpyrrolidone.

Claim 15. The transdermal therapeutic system of claim 14 wherein the hydrophilic polymer is soluble polyvinylpyrrolidone, and wherein the soluble polyvinylpyrrolidone is present in the active substance-containing matrix layer at a concentration of between 1.5 and 5% (w/w).

NEUPRO® transdermal systems: As illustrated in Exhibit E, the NEUPRO® transdermal systems contain between 1.5 and 5% (w/w) povidone. As provided in Exhibit I, povidone is synonymous with polyvinylpyrrolidone.

(10) **A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services . . . to determine the applicable regulatory review period as follows:**

(i) **For a patent that claims a human drug. . . product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) . . . was initially submitted and the NDA . . . number, and the date on which the NDA was approved . . . .**

The Investigational New Drug Application ("IND 47,852") for the approved product, the NEUPRO® (rotigotine) transdermal systems, was submitted to the FDA on 26 April 1995. A copy of the letter transmitting IND 47,852 to the FDA is attached as Exhibit J. The FDA accorded IND 47,852 a date of receipt of 27 April 1995. A copy of the letter from the FDA acknowledging receipt of IND 47,852 is attached as Exhibit K. Accordingly, IND 47,852 became effective on 27 May 1995.

The New Drug Application ("NDA 21-829") for the approved product, NEUPRO® (rotigotine) transdermal systems, was submitted to the FDA on 19 January 2005. A copy of the letter transmitting NDA 21-829 to the FDA is attached as Exhibit L. The FDA accorded NDA 21-829 a date of receipt of 28 January 2005. A copy of the letter from the FDA acknowledging receipt of NDA 21-829 is attached as Exhibit M.

The NDA 21-829 for the approved product, NEUPRO® (rotigotine) transdermal systems, was approved on 9 May 2007. A copy of the approval letter from the FDA is attached as Exhibit F.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

A description of significant activities undertaken by the marketing applicant, Schwarz BioSciences, Inc., during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities are set forth in Exhibit N. Exhibit N is divided into two parts as follows: (1) IND 47,852 Chronology and (2) NDA 21-829 Chronology.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.

In the opinion of Applicant, U.S. Patent No. 6,884,434 is eligible for patent term extension under the provisions of U.S.C. §156. Specifically, Applicant believes that the requirements of 35 U.S.C. §156 for an extension of patent term are satisfied as follows:

(a) Statement of eligibility of the patent for extension under 35 U.S.C. 156(a):

Section 156(a) provides, in relevant part, that the "term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended . . . if (1) the term of the patent has not expired before an application for extension is submitted, (2) the term of the patent has never been extended under . . . [35 U.S.C. 156](e)(1) . . .; (3) [the] application for extension is submitted by the owner of record of the patent or its agent in accordance with . . . [35 U.S.C. 156](d); (4) the product has been subject to a regulatory review period before its commercial marketing or use; [and] (5) . . . the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred . . . . "

As described below by corresponding number, each of elements (1) through (5) has been satisfied.

(1) The term of U.S. Patent No. 6,884,434 expires 18 March 2019, based on a term which is 20 years from the filing date of the patent application. Therefore, this application has been submitted before the expiration of the patent term.

(2) The term of U.S. Patent No. 6,884,434 has not been extended heretofore.

(3) This application is submitted by Schwarz Pharma Limited, being successor in interest from Aderis Pharmaceuticals, Inc., as well as being a licensee of co-owner LTS Lohmann Therapie-Systeme AG, of U.S. Patent No. 6,884,434, through undersigned counsel of Schwarz Pharma Limited. This application further complies with the provisions of 35 U.S.C. 156(d) in that it is submitted within the sixty day period beginning on the date (9 May 2007) the product was approved for marketing under the FFDCA, and contains the information required under 35 U.S.C. 156(d).

(4) As evidenced by the letter dated 09 May 2007 from the FDA (see Exhibit F), the approved product was subject to a regulatory review period under Section 505(b) of the FFDCA before its commercial marketing or use.

(5) The permission for commercial marketing of NEUPRO® (rotigotine) transdermal systems, after regulatory review under Section 505(b) of the FFDCA is the first permitted commercial marketing of rotigotine. This is confirmed by the absence of any other approved new drug application under which rotigotine could be commercially marketed.

(b) Calculation of Extension Period:

The term of U.S. Patent No. 6,884,434 should be extended by 744 days. The term of the extension was determined as follows, using the Patent and Trademark Office form for "Calculation of Length of Patent Term Extension for a Human Drug Product" as provided in Exhibit O. The relevant dates used to calculate the patent term extension are as follows:

- IND 47,852 became effective on 26 May 1995
- U.S. Patent No. 6,884,434 license Aderis Pharmaceuticals, Inc. to Schwarz Pharma AG effective 17 July 1998
- IND 47,852 transfer to Schwarz Pharma Inc. effective 16 October 1998
- U.S. Patent No. 6,884,434 license LTS Lohmann Therapie-Systeme AG to Schwarz Pharma AG effective 25 January 1999
- U.S. Patent No. 6,884,434 licenses from Aderis Pharmaceuticals, Inc and LTS Lohmann Therapie-Systeme AG assigned to Schwarz Pharma Limited effective 30 December 2002
- NDA 21-829 submitted to the FDA on 19 January 2005
- 6,884,434 issued on 26 April 2005
- Assignment of U.S. Patent 6,884,434 rights from Aderis Pharmaceuticals, Inc. to Schwarz Pharma Limited effective 14 July 2005
- NDA 21-829 approved on 9 May 2007

As provided in 35 U.S.C. 156(g)(1)(B), the regulatory review period is the sum of the two periods disclosed in subparagraphs (a) and (b) below.

(a) 35 U.S.C. 156(g)(1)(B)(i) Period (the "Testing Period"):

The period beginning on the date a §505(i) exemption became effective for the approved product (27 May 1995) and ending on the date a §505 application was initially submitted for the approved product (19 January 2005). The license from Aderis Pharmaceuticals, Inc. to Schwarz Pharma AG became effective on 17 July 1998. Therefore, the Testing Period between 17 July 1998 and 19 January 2005 is 2379 days.

(b) 35 U.S.C. 156(g)(1)(B)(ii) Period (the "Approval Period"):

The period beginning on the date a §505 application was initially submitted for the approved product (19 January 2005) and ending on the date such application was approved (09 May 2007) is a total of 841 days.

(13) A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (see § 1.765).

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information that is material to the determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon the application for extension (see §1.20(j)).

The Commissioner of Patents and Trademarks is authorized to charge the prescribed $1,120.00 fee set forth in 37 C.F.R. 1.20(j) for receiving and acting upon this Application for Extension of Patent Term, together with any additional fees that may be required during the entire pendency of this Application for Extension of Patent Term, to Deposit Account No. 08-0750. A Fee Transmittal (PTO/SB/17) expressly authorizing the charging of fees to Deposit Account No. 08-0750 in this matter is begin submitted in duplicate with the pending Application for Extension of Patent Term.

(15) **The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.**

Please direct all inquiries and correspondence relating to the application for patent term extension to:

J. Timothy Keane
Harness, Dickey & Pierce, PLC
7700 Bonhomme Avenue, Suite 400
Clayton, Missouri 63105
Telephone: (314) 726-7518
Fascimile: (314) 726-7501

(b) The application under this section must be accompanied by two additional copies of such application (for a total of three copies)

The present Application for Extension of Patent Term for U.S. Patent No. 6,884,434 is being submitted as one original and two additional copies thereof.

Respectfully submitted,

J. Timothy Keane

J. Timothy Keane
Registration No. 27,808

Date: July 5, 2007

CERTIFICATE OF HAND DELIVERY

The undersigned certifies that one original and two duplicate copies of this APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156 (including all Exhibits and supporting papers) are being hand-delivered this 6th day of July, to "Attention: Assistant Commissioner of Patents, Box Patent Extension, Washington, D.C. 20231", Office of Patent Legal Administration, United States Patent and Trademark Office.

Victoria Messenger
Schellin & Associates, Ltd.
#6409
1940 Duke Street, Suite 200
Alexandria, VA 22314

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	U.S. Patent No. 6,884,434
Title:	TRANSDERMAL THERAPEUTIC SYSTEM WHICH CONTAINS A D2 AGAONIST AND WHICH IS PROVIDED FOR TREATING PARKINSONISM, AND A METHOD FOR THE PRODUCTION THEREOF
Issue Date:	26 April 2005
Inventors:	Walter Muller and James V. Peck
Assignee and Owner:	LTS Lohmann Therapie-Systeme AG and Schwarz Pharma Limited
Licensee and Agent:	Schwarz Pharma Limited

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156
EXHIBIT LIST

A. Assignment to Discovery Therapeutics, Inc. and LTS Lohmann Therapie-Systeme AG
B. Change of Name from Discovery Therapeutics, Inc. to Aderis Pharmaceuticals, Inc.
C. Assignment to Schwarz Pharma Limited
D. Powers of Attorney from LTS Lohmann Therapie-Systeme AG and Schwarz Pharma AG on behalf of Schwarz Pharma Limited
E. Approved NEUPRO® Transdermal System Package Insert and Patient Package Insert
F. NDA Approval Letter dated 9 May 2007
G. U.S. Patent No. 6,884,434
H. NEUPRO® Transdermal System Description (Redacted)
I. Povidone entry from Pharmaceutical Excipients Handbook
J. Letter Transmitting IND 47,852 to FDA
K. FDA Letter Acknowledging Receipt of IND 47,852
L. Letter Transmitting NDA 21-829 to FDA
M. FDA Letter Acknowledging Receipt of NDA 21-829
N. Description of Significant Activities
O. PTE Calculation Sheet

EXHIBIT A

Attorney Docket No.: FLA-0048

A S S I G N M E N T

WHEREAS, we Walter Müller and James V. Peck, hereinafter referred to as the assignors, residing respectively at Engerser Strasse 56, Nauwied, Germany and 10821 Millington Lane, Richmond, Virgina are the joint inventors of certain inventions or improvements for which we have made application for Letters Patent to the United States, identified as Attorney Docket No. FLA-0048, entitled Transdermal Therapeutic System Which Contains a D2 Agonist and Which is Provided for Treating Parkinsonism, and a Method for the Production Thereof; and

WHEREAS, LTS LOHMANN THERAPIE-SYSTEME AG, of Andernach, Germany a corporation of Germany and DISCOVERY THERAPEUTICS, INC., of Richmond, Virginia, a corporation of Virginia, hereinafter referred to as assignees, are desirous of acquiring the entire right, title and interest in and to the said inventions or improvements and in and to the said application, and in, to and under any and all Letters Patent which may be granted on or as a result thereof in any and all countries:

NOW, THEREFORE, for and in consideration of the sum of One Dollar ($1.00) to each of us in hand paid by said assignees, and other good and valuable consideration, the receipt of which is hereby acknowledged, we, the said assignors, have sold, assigned, transferred and set over, and by these presents do hereby sell, assign, transfer and set over to said assignees, the entire right, title and interest in and to said inventions or improvements and said application and any and all continuations, divisions and renewals of and substitutes for said application, and in, to and under any and all Letters Patent which may be granted on or as a result thereof in the United States and any and all other countries, and any reissue or reissues or extension or extensions of said Letters Patent, and assign to and authorize said assignees, to file in our names applications for Letters Patent in all countries, the same to be held and enjoyed by said assignees, its successors, assigns, nominees or legal representatives, to the full end of the term or terms for which said Letters Patent respectively may be granted, reissued or extended, as fully and entirely as the same would have been held and enjoyed by us had this assignment, sale and transfer not been made.

AND we hereby covenant that we have full right to convey the entire interest herein assigned, and that we have not executed and will not execute any agreement in conflict herewith, and we further covenant and agree that we will each time request is made and without undue delay, execute and deliver all such papers as may be necessary or desirable to perfect the title to said inventions or

representatives, and each of us agrees to communicate to said assignee or to its nominee all known facts respecting said inventions or improvements, said application and said Letters Patent, to testify in any legal proceedings, to sign all lawful papers, to execute all disclaimers and divisional, continuing, reissue and foreign applications, to make all rightful oaths, and generally to do everything possible to aid said assignee, its successors, assigns, nominees and legal representatives to obtain and enforce for its or their own benefit proper patent protection for said inventions or improvements in any and all countries.

AND we hereby authorize and request the Commissioner of Patents and Trademarks of the United States and any official of any country or countries foreign to the United States whose duty it is to issue patents on applications as aforesaid, to issue to said assignee, as assignee of the entire right, title and interest, any and all Letters Patent for said inventions or improvements, including any and all Letters Patent of the United States which may be issued and granted on or as a result of the application aforesaid, in accordance with the terms of this assignment.

We further authorize and direct our attorneys to insert below* the serial number and filing date of said application now identified as Attorney Docket No. **FLA-0048** as soon as the same shall have been made known to them by the United States Patent Office.

IN WITNESS WHEREOF, we have hereunto set our hands and seals.

Walter Müller (L.S.)
WALTER MÜLLER

Witnessed by:

Dr. Jo. Leonhard Jo. Cl 1 Dated: 4.10.2000
(Please print)
Name: Radestr. 13
Address: D-56170 Bendorf

(Complete if signing before a Notary Public)

On this _____ day of _____, 2000, before me personally came the above named Walter Müller to me personally known and known to me to be the same individual who executed the foregoing assignment, and who acknowledged to me that execution of the same was of that person's own free will for the use and purposes therein set forth.

_____
Notary Public

James V. Peck (L.S.)
JAMES V. PECK

Witnessed by:

Sandra Montecalvo Dated: 11/20/00
(Please print)
Name: SANDRA Montecalvo
Address: 1927 Airy Circle
Richmond, VA 23233

(Complete if signing before a Notary Public)

On this _____ day of _____, 2000, before me personally came the above named James V. Peck to me personally known and known to me to be the same individual who executed the foregoing assignment, and who acknowledged to me that execution of the same was of that person's own free will for the use and purposes therein set forth.

_____
Notary Public

*The above assignment covers application Serial No. 09/647,290, filed on September 28, 2000.

The above insertion made by me this 28th day of November, 2000.

Jane Massey Licata

Jane Massey Licata, Reg. No. 32,257
of Law Offices of JANE MASSEY LICATA

EXHIBIT B

/

Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "DISCOVERY THERAPEUTICS, INC.", CHANGING ITS NAME FROM "DISCOVERY THERAPEUTICS, INC." TO "ADERIS PHARMACEUTICALS, INC.", FILED IN THIS OFFICE ON THE FOURTH DAY OF JANUARY, A.D. 2002, AT 9 O'CLOCK A.M.

A FILED COPY OF THIS CERTIFICATE HAS BEEN FORWARDED TO THE NEW CASTLE COUNTY RECORDER OF DEEDS.

2391828 8100

020005159

Harriet Smith Windsor

Harriet Smith Windsor, Secretary of State

AUTHENTICATION: 1539389

DATE: 01-04-02

PATENT

CERTIFICATE OF AMENDMENT OF AMENDED AND RESTATED CERTIFICATE OF INCORPORATION OF DISCOVERY THERAPEUTICS, INC., a Delaware corporation

Discovery Therapeutics, Inc., a corporation organized and existing under and by virtue of the General Corporation Law of the State of Delaware (the "Company"), DOES HEREBY CERTIFY:

1. That the Board of Directors of this Corporation, acting pursuant to the authority of Section 141(f) of the General Corporation Law of the State of Delaware, adopted a resolution setting forth a proposed amendment of the Amended and Restated Certificate of Incorporation of this Corporation. The resolution setting forth the proposed amendment is as follows:

NOW, THEREFORE, BE IT RESOLVED, that the Amended and Restated Certificate of Incorporation of the Company be further amended by changing Article I thereof so that, as amended, Article I shall read in its entirety as follows:

"I.

The name of the corporation is Aderis Pharmaceuticals, Inc."

2. That in lieu of a meeting and vote of stockholders, the stockholders of this Corporation entitled to vote have given written consent to said amendment in accordance with the provisions of Section 228 of the General Corporation Law of the State of Delaware.

3. That the above amendment was duly adopted in accordance with the applicable provisions of Sections 228 and 242 of the General Corporation Law of the State of Delaware.

STATE OF DELAWARE
SECRETARY OF STATE
DIVISION OF CORPORATIONS
FILED 09:00 AM 01/04/2007
070005159 – 3391526

IN WITNESS WHEREOF, the undersigned has caused this Certificate of Amendment to be signed by Peter G. Savas, its President and Chief Executive Officer, this 4th day of January, 2002.

DISCOVERY THERAPEUTICS, INC.
a Delaware corporation

By: _____
Peter G. Savas
President and Chief Executive Officer

oc_documents\3[W2000]

PAT

EXHIBIT C

ASSIGNMENT OF PATENT AND INVENTION RIGHTS

This Assignment of Patent Rights (the "Agreement") is entered into as of July 14, 2005 (the "Effective Date"), by and between Aderis Pharmaceuticals, Inc., a Delaware corporation ("Assignor"), and Schwarz Pharma Limited, an Irish limited company ("Assignee").

WHEREAS, Assignor is the owner of all right, title, and interest in and to (i) the U.S. patents and patent applications specified in Schedule A attached hereto, all corresponding foreign patents and patent applications, including, without limitation, those specified in Schedule A attached hereto, and all inventions disclosed and/or claimed in those patents and applications, (ii) an undivided interest, together with the co-owner(s) identified in Schedule B hereto, in and to the U.S. patents and patent applications specified in Schedule B attached hereto, in all corresponding foreign patents and patent applications, including, without limitation, those specified in Schedule B attached hereto, and all inventions disclosed and/or claimed in those patents and applications, and (iii) all rights that may exist in and to the abandoned, lapsed, or expired U.S. patents and patent applications specified in Schedule C attached hereto, all corresponding foreign patents and patent applications, including, without limitation, those specified in Schedule C attached hereto, and all inventions disclosed and/or claimed in those patents and applications, (collectively, the "Patent and Invention Rights");

WHEREAS, Assignee is desirous of acquiring the entire and exclusive right, title and interest in and to the Patent and Invention Rights in the United States and throughout the world; and

WHEREAS, Assignor is willing to assign to Assignee all rights, title and interest in and to the Patent and Invention Rights in the United States and throughout the world.

NOW, THEREFORE, for good and valuable consideration, receipt of which is hereby acknowledged by Assignor, Assignor hereby unconditionally assigns, transfers and conveys to Assignee, and Assignee hereby accepts, all of Assignor's right, title and interest throughout the world in and to the Patent and Invention Rights, all existing and future design modifications and improvements thereon, and any and all Letters Patent whether U.S. or foreign that are or may be granted therefrom including without limitation any extensions, continuations, continuations-in-part, divisions, reissues, reexaminations, revived or reinstated applications, reinstated or revived patents, term extensions, and renewals thereof, or other equivalents thereof, and further, all rights and privileges pertaining to the Patent and Invention Rights and any and all Letters Patent whether U.S. or foreign that are or may be granted therefrom including, without limitation, the right, if any, to sue or bring other actions for past, present and future infringement thereof.

Assignor further unconditionally assigns to and empowers Assignee, its successors, assigns or nominees, all rights to (i) make, revive, or reinstate applications for patents, (ii) reinstate or revive abandoned, lapsed, or expired patents, (iii) or seek and obtain other forms of protection for said inventions, design modifications and improvements and to prosecute such applications or petitions for revival and reinstatement as well as to claim and receive the benefit of the right of priority provided by the International Convention for the Protection of Industrial Property, as amended, or by any convention which may henceforth be substituted for it, and the right to invoke and claim such right of priority without further written or oral authorization.

This Agreement shall be governed by the laws of the State of New York (regardless of the laws that might otherwise govern under applicable New York principles of conflicts of law) as to all matters, including but not limited to matters of validity, construction, effect, performance and remedies.

This Agreement and all of the provisions hereof shall be binding upon and inure to the benefit of the Parties and their respective successors and assigns.

Each party represents that it has taken all necessary action to authorize the execution and delivery of this Agreement.

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be executed by their respective duly authorized officers, as of the Effective Date.

ADERIS PHARMACEUTICALS, INC.:

By: _____
Title: VP
Date: 7-19-05

SCHWARZ PHARMA LIMITED:

By: _____
Title: _____
Date: _____

On this 14 day of July, 2005, before me appeared Kenneth L. Rice, the person who signed this instrument, who acknowledged that he/she signed it as a free act on his/her own behalf or on behalf of the Assignor with authority to do so.

State of Massachusetts)
) ss.
County of Middlesex)

MICHELLE WERNER
Notary Public
Commonwealth of Massachusetts
My Commission Expires
December 3, 2010

Michelle Werner

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be executed by their respective duly authorized officers, as of the Effective Date.

ADERIS PHARMACEUTICALS, INC.:

By: _____
Title: _____
Date: _____

SCHWARZ PHARMA LIMITED:

By: _____
Title: DIRECTOR
Date: July 14, 2005

DIRECTOR

On this _____ day of July, 2005, before me appeared _____, the person who signed this instrument, who acknowledged that he/she signed it as a free act on his/her own behalf or on behalf of the Assignor with authority to do so.

State of _____)
) ss.
County of _____)

SCHEDULE A

U.S. Patent / Appl. No.	U.S. Filing Date	U.S. Issue Date	Foreign Equivalents	Patent No./Appl. No.
4,885,308	6/13/88	12/5/89	Japan	[redacted]
			Canada	[redacted]
			South Korea	[redacted]
5,177,112	9/10/91	1/5/93	Not Filed	n/a
6,372,920	11/16/00	4/16/02	European patent designating: Austria, Belgium, Switzerland/Liechtenstein, Cyprus, Germany, Denmark, Spain, Finland, France, Great Britain, Greece, Ireland, Italy, Luxemburg, Monaco, Netherlands, Portugal, Sweden, and Turkey	[redacted]
			Canada	[redacted]
			China	[redacted]
			Hong Kong	[redacted]
			Poland	[redacted]

5,382,596	8/5/93	1/17/95	European patent designating: Austria, Belgium, Switzerland, Liechtenstein, Germany, Denmark, Ireland, France, Great Britain, Italy, Luxemburg, Monaco, Netherlands, Portugal, Spain, Sweden, and Greece	0717620
			Japan	[redacted]
			Canada	[redacted]
			Australia	[redacted]

SCHEDULE B

U.S. Patent / Appl. No.	U.S. Filing Date	U.S. Issue Date	Foreign Equivalents	Patent No./Appl. No.
6,884,434	3/18/99 (PCT filing date)	4/26/05	EPO (17 contracting states + extension state Slovenia)	1033978
			Japan	2002509878
			Canada	2326630
			Australia	746856
			Brazil	9909313
			China/Hong Kong	11427763/ 1031196
			Indonesia	ID 000 9922
			Israel	138722
			Mexico	223211
			New Zealand	507066
			Norway	200004915
			Poland	343255
			Singapore	76365
			Slovakia	200001446
			South Korea	0432276
			Turkey	200002829
			Czech Republic	PV 2000-3581
			Hungary	200101519
			Argentina	P99010 1336
			Philippines	1-1999-00666
			Malaysia	PI 99 01191
			South Africa	200005261
			Taiwan	579299
10/936,620 published as [illegible] (continuation of U.S. Pat. No 6,884,434)	09/7/04		Foreign counterparts are the same as for U.S. Pat. No. 6,884,434	See above

SCHEDULE C

Application Number	Patent Number	Grant Date	Title
06/600,009	4,540,691	9/10/1985	NOVEL DOPAMINE AGONISTS
85902262.6	0179855	7/29/1992	NOVEL DOPAMINE AGONISTS
42339/85			NOVEL DOPAMINE AGONISTS
85902262.6	0179855	7/29/1992	NOVEL DOPAMINE AGONISTS
478,967	1,264,741	1/23/1990	NOVEL DOPAMINE AGONISTS
85902262.6	0179855	7/29/1992	NOVEL DOPAMINE AGONISTS
85902262.6	P3586411.7-085	7/29/1992	NOVEL DOPAMINE AGONISTS
85902262.6	0179855	7/29/1992	NOVEL DOPAMINE AGONISTS
542,229	542229	5/11/1987	NOVEL DOPAMINE AGONISTS
85902262.6	0179855	7/29/1992	NOVEL DOPAMINE AGONISTS
85902262.6	0179855	7/29/1992	NOVEL DOPAMINE AGONISTS
939/85	58384	9/8/1993	NOVEL DOPAMINE AGONISTS
85902262.6	0179855	7/29/1992	NOVEL DOPAMINE AGONISTS
501868/1985			NOVEL DOPAMINE AGONISTS
85902262.6	0179855	7/29/1992	NOVEL DOPAMINE AGONISTS
85902262.6	0179855	7/29/1992	NOVEL DOPAMINE AGONISTS
PCT/US85/00644			NOVEL DOPAMINE AGONISTS
85902262.6	0179855	7/29/1992	NOVEL DOPAMINE AGONISTS
85/2704	85/2704	12/24/1985	NOVEL DOPAMINE AGONISTS
06/455,144			SUBSTITUTED 2-AMINOTETRALINS AND PROCESS FOR SYNTHESIS
06/640,685	4,564,628	1/14/1986	SUBSTITUTED 2-AMINOTETRALINS

Application Number	Patent Number	Grant Date	Title
06/811,768	4,657,925	4/14/1987	METHOD AND COMPOSITIONS FOR REDUCING THE INTRAOCULAR PRESSUR E OF MAMMALS
06/839,976	4,722,933	2/2/1988	SUBSTITUTED 2-AMINOTETRALINS
06/891,200			METHOD AND COMPOSITIONS FOR REDUCING THE INTRAOCULAR PRESSUR E OF MAMMALS
06/891,223			SUBSTITUTED 2-AMINOTETRALINS
06/891,262	4,743,618	5/10/1988	SUBSTITUTED 2-AMINOTETRALINS
07/047,882	4,882,352	11/21/1989	METHOD FOR TREATING SCHIZOPHRENIA
07/313,483			METHOD AND COMPOSITIONS FOR REDUCING THE INTRAOCULAR PRESSURE OF MAMMALS
07/361,139			SUBSTITUTED 2-AMINOTETRALINS
07/371,207			SUBSTITUTED 2-AMINOTETRALINS
07/397,749	4,998,228	2/26/1991	METHOD AND COMPOSITIONS FOR TREATMENT OF PARKINSONISM SYNDROME IN MAMMALS
07/438,357			METHOD FOR TREATING SCHIZOPHRENIA
07/757,336	5,177,112	1/5/1993	SUBSTITUTED 2-AMINOTETRALINS
07/793,848	5,268,385	12/7/1993	METHOD FOR TREATING SCHIZOPHRENIA
07/951,993	5,256,661	10/26/1993	SUBSTITUTED 2-AMINOTETRALINS AND PHARMACEUTICAL USE

Application Number	Patent Number	Grant Date	Title
71604/87	597642	12/7/1990	SUBSTITUTED 2-AMINOTETRALINS
76198/87			METHOD AND COMPOSITIONS FOR REDUCING THE INTRAOCULAR PRESSURE OF MAMMALS
76197/87	605777	5/16/1991	SUBSTITUTED 20AMINOTETRALINS
17922/88	601596	1/15/1991	METHOD FOR TREATING SCHIZOPHRENIA
37377/89	628353	2/4/1993	METHOD AND COMPOSITIONS FOR TREATMENT OF PARKINSONISM SYNDROME IN MAMMALS
84105843.1	0168505	8/9/1989	SUBSTITUTED 2-AMINOTETRALINS AND PROCESS FOR SYNTHESIS
454,789	1,248,537	1/10/1989	SUBSTITUTED 2-AMINOTETRALINS AND PROCESS FOR SYNTHESIS
532,096	1,286,681	7/23/1991	SUBSTITUTED 2-AMINOTETRALINS
538,493			METHOD AND COMPOSITIONS FOR REDUCING THE INTRAOCULAR PRESSURE OF MAMMALS
537,476			SUBSTITUTED 20AMINOTETRALINS
566,096			METHOD FOR TREATING SCHIZOPHRENIA
84105843.1	0168505	8/9/1989	SUBSTITUTED 2-AMINOTETRALINS AND PROCESS FOR SYNTHESIS
84105843.1	0168505	8/9/1989	SUBSTITUTED 2-AMINOTETRALINS AND PROCESS FOR SYNTHESIS

Application Number	Patent Number	Grant Date	Title
84105843.1	0168505	8/9/1989	SUBSTITUTED 2-AMINOTETRALINS AND PROCESS FOR SYNTHESIS
88117733.5			METHOD AND COMPOSITIONS FOR REDUCING THE INTRAOCULAR PRESSURE OF MAMMALS
87902225.9			SUBSTITUTED 2-AMINOTETRALINS
87110342.0			METHOD AND COMPOSITIONS FOR REDUCING THE INTRAOCULAR PRESSURE OF MAMMALS
87110341.2	0254989	9/26/1990	SUBSTITUTED 2-AMINOTETRALINS
88904866.6			METHOD FOR TREATING SCHIZOPHRENIA
89906558.5			METHOD AND COMPOSITIONS FOR TREATMENT OF PARKINSONISM SYNDROME IN MAMMALS
533227	533227	3/6/1985	SUBSTITUTED 2-AMINOTETRALINS AND PROCESS FOR SYNTHESIS
84105843.1	0168505	8/9/1989	SUBSTITUTED 2-AMINOTETRALINS AND PROCESS FOR SYNTHESIS
84105843.1	0168505	8/9/1989	SUBSTITUTED 2-AMINOTETRALINS AND PROCESS FOR SYNTHESIS
1281/84	57491	3/10/1993	SUBSTITUTED 2-AMINOTETRALINS AND PROCESS FOR SYNTHESIS
84105843.1	0168505	8/9/1989	SUBSTITUTED 2-AMINOTETRALINS AND PROCESS FOR SYNTHESIS
111096/84	1817555	1/27/1994	SUBSTITUTED 2-AMINOTETRALINS AND PROCESS FOR SYNTHESIS

Application Number	Patent Number	Grant Date	Title
503621/86			METHOD AND COMPOSITIONS FOR REDUCING THE INTRAOCULAR PRESSURE OF MAMMALS
502102/87			SUBSTITUTED 2-AMINOTETRALINS
188674/87			METHOD AND COMPOSITIONS FOR REDUCING THE INTRAOCULAR PRESSURE OF MAMMALS
188675/87			SUBSTITUTED 2-AMINOTETRALINS
504581/88			METHOD FOR TREATING SCHIZOPHRENIA
700015/1989			METHOD FOR TREATING SCHIZOPHRENIA
84105843.1	0168505	8/9/1989	SUBSTITUTED 2-AMINOTETRALINS AND PROCESS FOR SYNTHESIS
PCT/US87/00491			SUBSTITUTED 2-AMINOTETRALINS
PCT/US88/01540			METHOD FOR TREATING SCHIZOPHRENIA
PCT/US89/02445			METHOD AND COMPOSITIONS FOR TREATMENT OF PARKINSONISM SYNDROME IN MAMMALS
84105843.1	0168505	8/9/1989	SUBSTITUTED 2-AMINOTETRALINS AND PROCESS FOR SYNTHESIS
07/216,405	4,931,270	6/5/1990	METHOD FOR DETECTING DOPAMINERGIC DISEASES USING FLUORINE-18 RADIOLABELLED D2 DOPAMINE RECEPTOR LIGANDS

Application Number	Patent Number	Grant Date	Title
07/220,528			FLUORINE-18 RADIOLABELLED D1 DOPAMINE RECEPTOR LIGANDS AND A METHOD FOR THEIR SYNTEHSIS
07/336,708			A METHOD OF REDUCING BODY WEIGHT AND FOOD INTAKE USING A DOPAMINE D2 RECEPTOR AGONIST
07/375,583			SUBSTITUTED 2-AMINOTETRALINS
07/837,229	5,274,003	12/28/1993	SUBSTITUTED 2-AMINOTETRALINS
08/131,845	5,358,971	10/25/1994	SUBSTITUTED 2-AMINOTETRALINS
08/200,338	5,430,056	7/4/1995	SUBSTITUTED 2-AMINOTETRALINS
60720/90			SUBSTITUTED 2-AMINOTETRALINS
2,085,450			SUBSTITUTED 2-AMINOTETRALINS
90911220.3			SUBSTITUTED 2-AMINOTETRALINS
National phase not timely entered			SUBSTITUTED 2-AMINOTETRALINS
PCT/US90/03761			SUBSTITUTED 2-AMINOTETRALINS
07/401,060			SUBSTITUTED 2-AMINOTETRALINS USEFUL AS DOPAMINERGICS
07/758,887	5,118,704	6/2/1992	SUBSTITUTED 2-AMINOTETRALINS USEFUL AS DOPAMINERGICS
90913967.7			SUBSTITUTED 2-AMINOTETRALINS USEFUL AS DOPAMINERGICS
PCT/US90/04734			SUBSTITUTED 2-AMINOTETRALINS USEFUL AS DOPAMINERGICS

Application Number	Patent Number	Grant Date	Title
07/538,847			SUBSTITUTED NAPHTHOXAZINES USEFUL AS DOPAMINERGICS
82249/91	651608	11/15/1994	SUBSTITUTED NAPHTHOXAZINES USEFUL AS DOPAMINERGICS
2083146			SUBSTITUTED NAPHTHOXAZINES USEFUL AS DOPAMINERGICS
91913320.7			SUBSTITUTED NAPHTHOXAZINES USEFUL AS DOPAMINERGICS
512413/91			SUBSTITUTED NAPHTHOXAZINES USEFUL AS DOPAMINERGICS
PCT/US91/04112			SUBSTITUTED NAPHTHOXAZINES USEFUL AS DOPAMINERGICS
07/669,856			SUBSTITUTED NAPHTHOXAZINES USEFUL AS DOPAMINERGICS
07/869,940			SUBSTITUTED NAPHTHOXAZINES USEFUL AS DOPAMINERGICS
PCT/US93/05305			SUBSTITUTED NAPHTHOXAZINES USEFUL AS DOPAMINERGICS
P 000108058			IMPROVED PROCESS FOR PREPARING NITROGEN-SUBSTITUTED AMINOTETRALINS
P3417659.7			SELECTOR D-2 DOPAMINE RECEPTOR AGONIST
532579	532579	9/20/1985	SELECTOR D-2 DOPAMINE RECEPTOR AGONIST
6407057	2563731	3/24/1989	SELECTOR D-2 DOPAMINE RECEPTOR

Application Number	Patent Number	Grant Date	Title
			AGONIST
8411483	2157950	11/2/1988	SELECTOR D-2 DOPAMINE RECEPTOR AGONIST
20833A/84			SELECTOR D-2 DOPAMINE RECEPTOR AGONIST
100334/84			SELECTOR D-2 DOPAMINE RECEPTOR AGONIST

EXHIBIT D

POA (b)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No. 6,884,434

Issue Date: April 26, 2005

To: Walter Muller and James V. Peck

Title: Transdermal Therapeutic System Which Contains A D_2 Agonist And Which Is Provided For Treating Parkinsonism, And A Method For The Production Thereof

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

POWER OF ATTORNEY

Sir:

LTS Lohmann Therapie-Systeme AG, a German corporation, having offices at Lohmannstraße 2, D-56626 Andernach, Germany, being co-owner of entire right, title and interest in and to U.S. Patent No. 6,884,434, which was granted on April 26, 2005 to Walter Muller and James V. Peck, and entitled "Transdermal Therapeutic System Which Contains A D_2 Agonist And Which Is Provided For Treating Parkinsonism, And A Method For The Production Thereof", hereby appoints Schwarz Pharma AG, having offices at Alfred-Nobel-Straße 10 40789 Monheim, Germany, and Harness, Dickey & Pierce, PLC, having offices at 7700 Bonhomme, Suite 400, St. Louis, Missouri 63105, United States of America, as its agents to act in its interest in this matter, and also appoints the attorneys and agents associated with Customer No. **28997**, each of them with full power of substitution and revocation, with regard to an application for Patent Term Extension of U.S. Patent No. 6,884,434 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Please direct all telephone calls to J. Timothy Keane (Reg. #27,808) at 314-726-7518, and all correspondence to Harness, Dickey & Pierce, P.L.C., 7700 Bonhomme, Suite 400, St. Louis, Missouri 63105, United States of America.

LTS Lohmann Therapie-Systeme AG

By: ppa. _____ ppa. _____

Name: Dr. Bodo Asmussen Dr. Friedrich Grubenbecher

Title: (Head of research & development) (Head of key account management)

Date: July 04, 2007

POWER OF ATTORNEY
and
Change of Correspondence Address

U.S. Patent No. 6,884,434 **Issue Date:** April 26, 2005

Title: Transdermal Therapeutic System Which Contains A D_2 Agonist And Which Is Provided For Treating Parkinsonism, And A Method For The Production Thereof

Attorney Docket No.: 6102-000078/US

The undersigned:

Schwarz Pharma Limited
Industrial Estate
Shannon, County Clare, Republic of Ireland

hereby appoint(s) the following person(s):

Practitioners listed under Customer Number: **28997**

to represent the undersigned before the United States Patent and Trademark Office in connections with filing and prosecution of a Patent Term Extension application.

Further, the undersigned requests the Patent and Trademark Office to change the correspondence address for the above-identified patent to be associated with Customer No. 28997, Harness, Dickey & Pierce, P.L.C., 7700 Bonhomme, Suite 400, St. Louis, Missouri 63105, United States of America.

SCHWARZ PHARMA LIMITED:

Ken McCauley
Finance Director / Assistant Managing Director
Date: 04/07/07

Olaf Elbrecht
Director
5.17.07

EXHIBIT E

Neupro®

(Rotigotine Transdermal System)

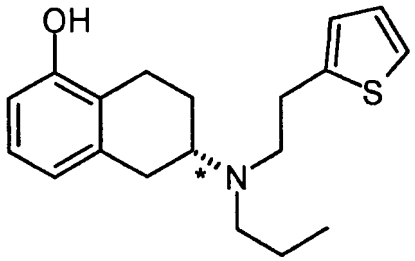
CONTINUOUS DELIVERY FOR ONCE-DAILY APPLICATION

Rx Only

DESCRIPTION

Neupro® (Rotigotine Transdermal System) is a transdermal delivery system that provides rotigotine, a non-ergolinic dopamine agonist. When applied to intact skin, Neupro is designed to continuously deliver rotigotine over a 24-hour period.

The chemical name of rotigotine is (6S)-6-{propyl[2-(2-thienyl)ethyl]amino}-5,6,7,8-tetrahydro-1-naphthalenol. The empirical formula is $C_{19}H_{25}NOS$. The molecular weight is 315.48. The structural formula for rotigotine is:



The asterisk designates the chiral center.

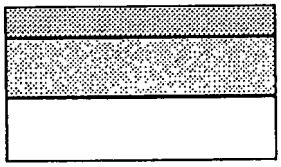
Neupro is available in three strengths: 2, 4, and 6 mg/24 hours. Each transdermal system has a release surface area of 10, 20, and 30 cm^2 and contains 4.5, 9, or 13.5 mg rotigotine, respectively. See Table 1. The composition of the transdermal system per area unit is identical.

Table 1 Transdermal System Size, Drug Content, and Nominal Delivery Rate

Neupro Nominal Dose	Rotigotine Content per System	Neupro System Size
2 mg/24 hours	4.5 mg	10 cm^2
4 mg/24 hours	9 mg	20 cm^2
6 mg/24 hours	13.5 mg	30 cm^2

System Components and Structure

Neupro is a thin, matrix-type transdermal system composed of three layers:



Backing film

Drug matrix

Protective liner

1. A flexible, tan-colored backing film, consisting of an aluminized polyester film coated with a pigment-layer on the outer side. The backing provides structural support and protection of the drug-loaded adhesive layer from the environment.
2. A self-adhesive drug matrix layer, consisting of the active component rotigotine and the following inactive components: ascorbyl palmitate, povidone, silicone adhesive, sodium metabisulfite, and dl-alpha-tocopherol.
3. A protective liner, consisting of a transparent fluoropolymer-coated polyester film. This liner protects the adhesive layer during storage and is removed just prior to application.

CLINICAL PHARMACOLOGY

Mechanism of Action

Rotigotine is a non-ergoline $D_3/D_2/D_1$ dopamine agonist for the treatment of Parkinson's disease. The precise mechanism of action of rotigotine as a treatment for Parkinson's disease is unknown although it is thought to be related to its ability to stimulate dopamine D2 receptors within the caudate-putamen in the brain. Rotigotine improved motor deficits in animal models of Parkinson's disease (6-OHDA in rat and MPTP model in monkey) including when administered transdermally

Pharmacokinetics

On average, approximately 45% of the rotigotine from the patch is released within 24 hours (0.2 mg/cm^2). Rotigotine is primarily eliminated in the urine as inactive conjugates. After removal of the patch, plasma levels decreased with a terminal half-life of 5 to 7 hours. The pharmacokinetic profile showed a biphasic elimination with an initial half-life of 3 hours.

Absorption

When single doses of 40 cm^2 systems are applied to the trunk, there is an average lag time of approximately 3 hours until drug is detected in plasma, (range 1 to 8 hours). Tmin occurs most commonly between 0 to 7 hours post dose. Tmax typically occurs between 15 to 18 hours post dose but can occur from 4 to 27 hours post dose. However, there is no characteristic peak concentration observed. Rotigotine displays dose-proportionality over a daily dose range of 2 mg/24 hours to 8 mg/24 hours.

On average, approximately 45% of the rotigotine from the patch is released within 24 hours (0.2 mg/cm^2), independent of patch size. Similar absorption per cm^2 was observed in healthy subjects and patients with early stage Parkinson's disease.

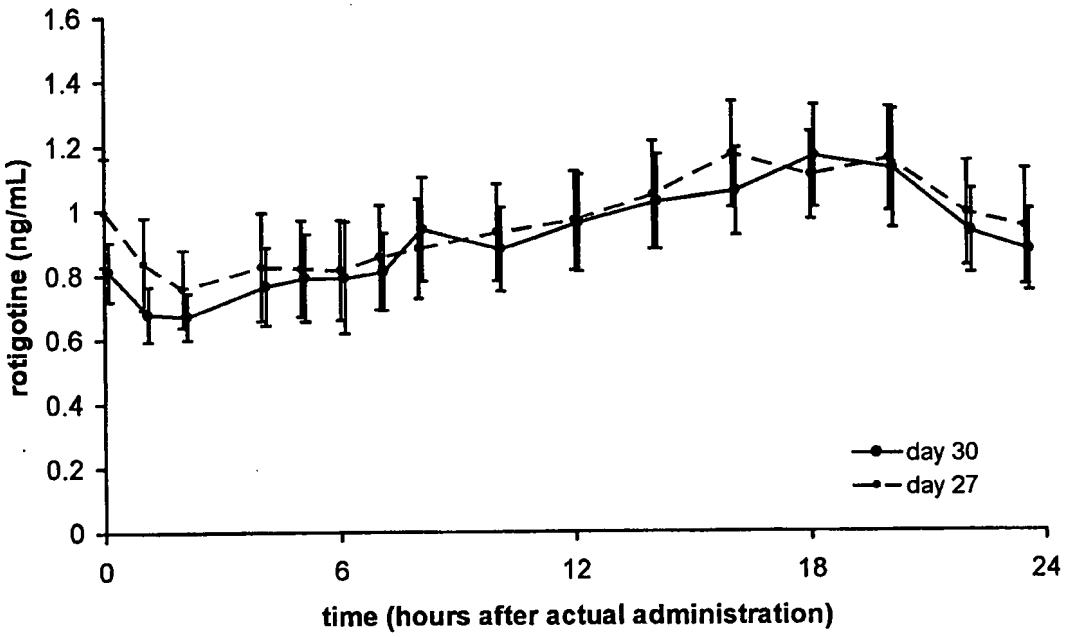
In the clinical studies of rotigotine effectiveness, the transdermal system application site was rotated from day to day (abdomen, thigh, hip, flank, shoulder, or upper arm) and the mean measured plasma concentrations of rotigotine were stable over the six months of maintenance treatment. Relative bioavailability for the different application sites at steady-state was evaluated in subjects with Parkinson's disease. Differences in bioavailability ranged from less

than 1% (abdomen vs hip) to 64% (shoulder vs thigh) with shoulder application showing higher bioavailability.

Because rotigotine is administered transdermally, food should not affect absorption, and the product may be administered without regard to the timing of meals.

In a 14-day clinical study with rotigotine administered to healthy subjects, steady-state plasma concentrations were achieved within 2 to 3 days of daily dosing.

Figure 1 Average (±95% CI) Neupro Plasma Concentrations in Patients with Early-Stage Parkinson's Disease After Application of 8 mg/24 hours to 1 of 6 Application Sites (shoulder, upper arm, flank, hip, abdomen, or thigh) on 2 Different Days During the Maintenance Phase



Distribution

The weight normalized apparent volume of distribution, (Vd/F), in humans is approximately 84 L/kg after repeated dose administration.

The binding of rotigotine to human plasma proteins is approximately 92% *in vitro* and 89.5% *in vivo*.

Metabolism and Elimination

Rotigotine is extensively metabolized by conjugation and N-dealkylation. After intravenous dosing the predominant metabolites in human plasma are sulfate conjugates of rotigotine, glucuronide conjugates of rotigotine, sulfate conjugates of the N-despropyl-rotigotine and

conjugates of N-desthienyl -rotigotine. Multiple CYP isoenzymes, sulfotransferases and two UDP-glucuronosyltransferases catalyze the metabolism of rotigotine (See Drug Interactions)

After removal of the patch, plasma levels decreased with a terminal half-life of 5 to 7 hours. The pharmacokinetic profile showed a biphasic elimination with an initial half-life of 3 hours.

Rotigotine is primarily excreted in urine (~71%) as inactive conjugates of the parent compound and N-desalkyl metabolites. A smaller proportion is excreted in feces (~11%). The major metabolites found in urine were rotigotine sulfate (16% to 22%of the absorbed dose), rotigotine glucuronide (11%-15%), and N-despropyl-rotigotine sulfate metabolite (14% to 20%) and N-desthienylethyl-rotigotine sulfate metabolite (10% to 21%). Approximately 11% is renally eliminated as other metabolites. A small amount of unconjugated rotigotine is renally eliminated (<1% of the absorbed dose).

Pharmacokinetics in Special Populations

Hepatic Insufficiency

The effect of impaired hepatic function on the pharmacokinetics of rotigotine has been studied in subjects with moderate impairment of hepatic function (Child Pugh classification – Grade B). There were no relevant changes in rotigotine plasma concentrations. No dose adjustment is necessary in subjects with moderate impairment of hepatic function. No information is available on subjects with severe impairment of hepatic function. (See **PRECAUTIONS, Hepatic Insufficiency**)

Renal Insufficiency

The effect of renal function on rotigotine pharmacokinetics has been studied in subjects with mild to severe impairment of renal function including subjects requiring dialysis compared to healthy subjects. There were no relevant changes in rotigotine plasma concentrations. In subjects with severe renal impairment not on dialysis, (i.e., creatinine clearance 15 to <30 ml/min), exposure to rotigotine conjugates was doubled. No dosage adjustment is recommended.

Gender

Female and male subjects and patients had similar plasma concentrations (body weight normalized).

Geriatric Patients

Plasma concentrations of rotigotine in patients 65 to 80 years of age were similar to those in younger patients, approximately 40 to 64 years of age. Although not studied, exposures in older subjects (> 80 years) may be higher due to skin changes with aging.

Pediatric Patients

The pharmacokinetics of rotigotine in subjects below the age of 18 years has not been established.

Race

The pharmacokinetic profile was similar in Caucasians, Blacks, and Japanese. No dose adjustment is necessary based on ethnicity.

Adhesion

Adhesion was examined in subjects with Parkinson's disease when patches were applied to rotating sites. Similar results were observed for the 4 mg/24 hours (20 cm^2), 6 mg/24 hours (30 cm^2), and 8 mg/24 hours (40 cm^2) patches. An adherence of ≥90% of the patch surface was observed in 71% to 82% of cases. A partial detachment of >10% was observed in 15% to 24% of cases. A complete detachment of the patch was observed in 3% to 5% of cases.

CLINICAL STUDIES

The effectiveness of Neupro in the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease was evaluated in three parallel group, randomized, double-blind placebo controlled studies conducted in the U.S. and abroad. These studies were conducted in patients who were not receiving concomitant dopamine agonist therapy and, who were either L-dopa naïve or off L-dopa for at least 28 days prior to baseline and were never on L-dopa for more than 6 months. Patients were excluded from the study if they had a history of pallidotomy, thalamotomy, deep brain stimulation, or fetal tissue transplant. Patients receiving selegiline, anticholinergic agents, or amantadine must have been on a stable dose for at least 28 days prior to baseline; they were to attempt to maintain that dose for the duration of the study.

The primary outcome assessment was the change from baseline for the combined scores for Part II (activities of daily living component) plus part III (motor component) of the Unified Parkinson's Disease Rating Scale (UPDRS). Part II of the UPDRS contains 13 questions relating to activities of daily living that are scored from 0 (normal) to 4 (maximal severity) for a maximum (worst) score of 52. Part III of the UPDRS contains 27 questions (for 14 items), each scored 0 (normal) to 4 (maximal severity). Part III is designed to assess the severity of the cardinal motor findings in patients with Parkinson's disease (e.g., tremor, rigidity, bradykinesia, postural instability), scored for different body regions, and has a maximum (worst) score of 108.

<u>Dose-Response Study</u>

This study was a randomized, double-blind, dose-response, multicenter, multinational study in which 316 early stage Parkinson's Disease patients were assigned to treatment with either placebo or one of several fixed doses (2 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, or 8 mg/24 hours) of Neupro, given as 1, 2, 3, or 4 2-mg patches for a period up to 11 weeks. The patches were applied to the upper abdomen and the sites of application were rotated on a daily basis. Patients underwent a weekly titration (increasing the number of 2 mg/24 hours patches or placebo patches at weekly intervals) over 4 weeks such that the target doses of Neupro were achieved for all groups by the end of 3 weeks and were administered over the fourth week of the titration phase. Patients then continued on treatment for a 7 week maintenance phase followed by a down titration during the last week. Two back titrations by a single patch (i.e. 2 mg/24 hours decrement of Neupro or placebo) at a time were permitted for intolerable adverse events.

The mean age of patients was approximately 60 years (range 33 to 83 years; approximately 36 % were ≥ 65 years) and the study enrolled more men (62 %) than women (39 %). Most patients (85 %) were Caucasian and most randomized patients (≥ 88 %) completed the full treatment period.

Mean baseline combined UPDRS (Parts II + III) scores were similar among all treatment groups, between 27.1 and 28.5 for all groups. Patients experienced a mean improvement (i.e. reductions) in the combined UPDRS (Parts II + III) from baseline to end of treatment (end of week 11 or last visit for patients discontinuing early) of -3.5, -4.5, -6.3, and -6.3 for the 2 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, and 8 mg/24 hours Neupro groups respectively and –1.4 for the placebo group. The difference from the placebo group for the mean change for each Neupro dose is shown in Table 2. Statistically significant mean changes reflecting dose-related improvement were observed at the three highest doses, and the 6 mg/24 hours and 8 mg/24 hours doses had a similar effect.

Table 2 Dose-Response Study: Mean Change in UPDRS (Parts II + III) from Baseline at End of Treatment for Intent-to-Treat Population

Neupro Nominal Dose	Rotigotine Content per System	Difference from placebo
2 mg/24 hours	4.5 mg	-2.1
4 mg/24 hours	9 mg	-3.1
6 mg/24 hours	13.5 mg	-4.9
8 mg/24 hours	18 mg	-5.0

North American Study

This study was a randomized, double-blind, multinational, flexible Neupro dose (2, 4, or 6 mg/24 hours), parallel group study in which 277 early stage, idiopathic Parkinson's Disease patients were assigned (2: 1 ratio) to treatment with Neupro or placebo for a period up to about 28 weeks. This study was conducted in 47 sites in North America (U.S. and Canada). Patches were applied to different body parts including upper or lower abdomen, thigh, hip, flank, shoulder, and/ or upper arm and patch application sites were to be rotated on a daily basis. Patients underwent a weekly titration (consisting of 2 mg/24 hours increments at weekly intervals) over 3 weeks to a maximal dose of 6 mg/24 hours depending on efficacy and tolerability, and then received treatment over a 24 week maintenance phase followed by a de-escalation over a period up to 4 days. Back/down titration by a single patch (i.e. 2 mg/24 hours decrement of Neupro or placebo) was permitted during the titration phase for intolerable adverse events but was not permitted during the maintenance phase (i.e., patients with intolerable adverse events had to leave the study). Primary efficacy data were collected after a treatment period of up to approximately 27 weeks.

The mean age of patients was approximately 63 years (range 32 to 86 years; approximately 45 % were $\geq$ 65 years), approximately two-thirds of all patients were men, and nearly all patients were Caucasian. Approximately 90 % of patients randomized to Neupro achieved a maximal daily dose of 6 mg/24 hours; 70 % maintained this dose for most (> 20 weeks) of the maintenance phase. Most enrolled patients ($\geq$ 81 %) completed the full treatment period.

Mean baseline combined UPDRS (Parts II + III) was similar in both groups (29.9 Neupro group, 30.0 placebo). Neupro treated patients experienced a mean change in the combined UPDRS (Parts II + III) from baseline to end of treatment (end of treatment week 27 or last visit for patients discontinuing early) of -4.0, and placebo treated patients showed a mean change from baseline of +1.39 , a difference (see Table 3)that was statistically significant.

Table 3 North American Study: Mean Change in UPDRS (Parts II + III) from Baseline at End of Treatment for Intent-to-Treat Population

Neupro Nominal Dose	Rotigotine Content per System	Difference from placebo
Up to 6 mg/24 hours	Up to 13.5 mg	-5.3

Foreign Multinational Study

This study was a randomized, double-blind, multinational, flexible Neupro dose (2 mg/24 hours, 4 mg/2 hours, 6 mg/24 hours, or 8 mg/24 hours), three arm, parallel group, study using a double-dummy treatment in which 561 early stage, Parkinson's Disease patients were assigned to treatment with either placebo or Neupro or active oral comparator in a ratio of 1: 2: 2 for a period up to about 39 weeks. This study was conducted in up to 81 sites in many countries outside of North America. Patches were applied to different body parts including upper or lower abdomen, thigh, hip, flank, shoulder, and/ or upper arm and patch application sites were to be rotated on a daily basis. Treatment with a patch and placebo was given to all patients in a double-blinded manner such that no one would know the actual treatment (i.e. Neupro, comparator, or placebo). Patients underwent a weekly dose escalation of patch (consisting of 2 mg/24 hours increments of Neupro or placebo) and a dose escalation of capsules of comparator or placebo over 13 weeks up to a maximal dose of 8 mg/24 hours of Neupro depending on achieving optimal efficacy or intolerability at a lower dose. Patients randomized to Neupro achieved the maximal dose of 8 mg/24 hours after a 4 week titration if maximal efficacy and intolerability had not occurred over a 4 week titration period. Patients then received treatment over a 24 week maintenance phase followed by a de-escalation over a period up to 12 days. A single back titration by a single patch (i.e. 2 mg/24 hours decrement of Neupro or placebo) or capsule was permitted during the titration phase for intolerable adverse events but was not permitted during the maintenance phase (i.e. patients with intolerable adverse events had to discontinue from this study). Primary efficacy data were collected after a treatment period of up to approximately 37 weeks of randomized treatment.

The mean age of patients was approximately 61 years (range 30 -86 years; approximately 41 % were $\geq$ 65 years), nearly 60 % of all patients were men, and nearly all patients were Caucasian. About 73 % of patients completed the full treatment period. The mean daily dose of Neupro was just less than 8 mg/24 hours and approximately 90 % of patients achieved the maximal daily dose of 8 mg/24 hours.

Mean baseline combined UPDRS (Parts II + III) was similar across all groups (33.2 Neupro, 31.3 placebo, 32.2 comparator). Neupro treated patients experienced a mean change in the combined UPDRS (Parts II + III) from baseline to end of treatment (end of treatment week 37 or last visit for patients discontinuing early) of - 6.83, and placebo treated patients showed a mean change from baseline of – 2.33 (see Table 4), a difference that was statistically significant.

Table 4 Foreign Multinational Study: Mean Change in UPDRS (Parts II + III) from Baseline at End of Treatment for Intent-to-Treat Population

Neupro Nominal Dose	Rotigotine Content per System	Difference from placebo
Up to 8 mg/24 hours	Up to 18 mg	-4.5

INDICATIONS AND USAGE

Neupro is indicated for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease.

The effectiveness of Neupro was demonstrated in randomized, controlled studies in patients with early-stage Parkinson's disease who were not receiving concomitant L-dopa therapy. (See **CLINICAL STUDIES)**

CONTRAINDICATIONS

Neupro is contraindicated in patients who have demonstrated hypersensitivity to rotigotine or the components of the transdermal system.

WARNINGS

Sulfite Sensitivity

Neupro contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Falling Asleep During Activities of Daily Living

Patients treated with Neupro have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Although many of these patients reported somnolence while on Neupro, some perceived no warning signs, such as excessive drowsiness, and believed that they were alert

immediately prior to the event. Some of these events have been reported as late as one year after initiation of treatment.

Somnolence is a common occurrence in patients receiving Neupro. Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of pre-existing somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities. Patients should be advised to exercise caution while driving, operating machines, or working at heights during treatment with Neupro. Patients who have already experienced somnolence and/or an episode of sudden sleep onset should not participate in these activities during treatment with Neupro.

Before initiating treatment with Neupro, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with Neupro such as concomitant sedating medications and the presence of sleep disorders. If a patient develops meaningful daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), Neupro should ordinarily be discontinued (see DOSAGE AND ADMINISTRATION for guidance on discontinuing Neupro). If a decision is made to continue Neupro, patients should be advised not to drive and to avoid other potentially dangerous activities. There is insufficient information to establish whether dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Hallucinations

In three double-blind, placebo-controlled studies in patients with early-stage Parkinson's disease who were not treated with L-dopa, 2.0% (13 of 649) of patients treated with Neupro reported hallucinations compared to 0.7% (2 of 289) of patients on placebo. Hallucinations were of sufficient severity to cause discontinuation of treatment in 0.2% (1 of 649) Neupro treated patients compared to 0% (0 of 289) on placebo.

PRECAUTIONS

General

Symptomatic Hypotension

Dopamine agonists, in clinical studies and clinical experience, appear to impair the systemic regulation of blood pressure, resulting in postural hypotension, especially during dose escalation. Parkinson's disease patients, in addition, appear to have an impaired capacity to respond to a postural challenge. For these reasons, Parkinson's patients being treated with dopaminergic agonists ordinarily (1) require careful monitoring for signs and symptoms of postural hypotension, especially during dose escalation, and (2) should be informed of this risk. (See **PRECAUTIONS, Information for Patients)**

The pooled analyses of a variety of adverse event terms suggestive of orthostatic hypotension in the three controlled efficacy studies showed the incidence of these events with Neupro 6 mg/24 hours was 5%vs 4% for placebo. Examination of systolic blood pressure -decreases of $\geq$20 mmHg at 3 minutes after arising showed an incidence of 5% for Neupro 6 mg/24 hours vs 4%

for placebo. In a separate analysis, decreases in systolic blood pressure from baseline at anytime of ≥40 mmHg in the supine position were seen in 7% of subjects who received Neupro 6 mg/24 hours and 4% for placebo.

An analysis of the dose response study using a variety of adverse event terms suggestive of orthostatic hypotension, including dizziness and postural dizziness, showed a 2 fold higher incidence of these events with Neupro (22 %) vs placebo (11 %). This increased risk was observed in a setting in which patients were very carefully titrated, and patients with clinically relevant cardiovascular disease or symptomatic orthostatic hypotension at baseline had been excluded from this study. The study showed a dose-related increased risk for mild-moderate systolic orthostatic hypotension (decrease of ≥ 20 mm Hg) at the end of the titration period (after 4 weeks treatment) with the highest recommended 6 mg/24 hours Neupro dose (6 %) vs placebo (3 %) or lower Neupro doses (2 mg/24 hours or 4 mg/24 hours 0 %). An increased dose-related risk (3 % for 4 and 6 mg/24 hours Neupro; 2 % for placebo and 2 mg/24 hours Neupro) of systolic orthostatic hypotension was also observed after 7 weeks of treatment.

Syncope

Syncope has been reported in patients using dopamine agonists, and for this reason patients should be alerted to the possibility of syncope. The reported incidence of syncope was no greater among those receiving Neupro (1%) than among those receiving placebo (1%). Because the studies of Neupro excluded patients with clinically relevant cardiovascular disease, it is not known to what extent the estimated incidence figures apply to Parkinson's disease patients as a whole. Therefore, patients with severe cardiovascular disease should be treated with caution.

Elevation of Heart Rate and Blood Pressure

Neupro on average increased heart rate by 2 to 4 bpm in rotigotine treated patients compared to placebo patients. Subjects who received Neupro in clinical studies had a slightly higher incidence of a heart rate exceeding 100 beats per minute (9% vs 7% of placebo subjects).

Neupro treatment was not associated with a consistent mean change in systolic and diastolic blood pressure. Subjects on Neupro had a higher incidence of systolic blood pressures >180 mm Hg and diastolic blood pressures >105 mmHg compared to placebo (SBP: 4% vs 2%; DBP: 9% vs 5%). In the Dose-Response study, there was a dose-related increase in systolic blood pressure increases ≥ 20 mm Hg at the highest recommended Neupro dose (6 mg/24 hours), 12 % vs 9 % for lower doses or placebo when standing at the final visit and 8 % vs 3 % for lower doses or placebo after changing from supine to standing at the final visit. These findings of blood pressure elevations should be considered when treating patients with cardiovascular disease.

Weight Gain and Fluid Retention

Subjects taking Neupro had a higher incidence (3%) of substantial weight gain (more than 10% of baseline weight) than placebo subjects (<1%). This weight gain was frequently associated with the development of peripheral edema, suggesting that Neupro may cause substantial fluid retention in some patients. Although the weight gain was usually well-tolerated in subjects observed in clinical studies, it could cause greater difficulty in patients who may be especially vulnerable to negative clinical consequences from fluid retention such as those with significant congestive heart failure or renal insufficiency.

Dyskinesia

Neupro may potentiate the dopaminergic side effects of L-dopa and may cause and/or exacerbate pre-existing dyskinesia. Dyskinesia was reported at a similar rate in patients treated with Neupro (0.5%) or placebo (0.3%).

Hepatic Insufficiency

No adjustment of the dose is needed in patients with moderate hepatic impairment (Child Pugh classification – Grade B). The pharmacokinetics of rotigotine have not been studied in patients with severe hepatic impairment.

Application Site Reactions

Application site reactions (ASRs) were reported at a greater frequency in the Neupro treated patients (37%, 239/649) than in placebo patients (14%, 40/289) in the three double-blind, placebo-controlled studies with Neupro.

In the Dose-Response study, ASRs exhibited a dose-response relationship for the highest recommended Neupro dose (6 mg/24 hours) not only during the whole study period (placebo 19 %, 2 mg/24 hours 24 %, 4 mg/24 hours 21 %, 6 mg/24 hours 34 %) but also in separate analyses of the titration period and of the maintenance period. ASRs as a cause for study discontinuation also showed a dose-response increased risk for the whole study period for 6 mg/24 hours Neupro vs other treatments (placebo 0%, 2 mg/24 hours 2 %, 4 mg/24 hours 0 %, 6 mg/24 hours 3 %).

Of ASRs in Neupro treated patients, most were mild or moderate in intensity. The signs and symptoms of these reactions generally were localized erythema, edema, or pruritus limited to the patch area and usually did not lead to dose reduction. About 5% of patients treated with Neupro in these studies discontinued as a result of an ASR. Generalized skin reactions (e.g., allergic rash, including erythematous, macular-papular rash, or pruritus), have been reported at lower rates than ASRs during the development of Neupro.

In a clinical study to investigate the cumulative human skin irritation of Neupro, daily rotation of Neupro application sites has been shown to reduce the incidence of ASRs in comparison to repetitive application to the same site. In a clinical study investigating the skin sensitizing potential of Neupro in 221 healthy subjects, no case of contact sensitization was observed. Localized sensitization reactions were observed in a study in normal volunteers with continuous rotating transdermal system application to a 2.5 cm^2 system, (0.5 mg/24 hours), after induction of maximal irritational stress by repetitive transdermal system application to the same site. If a patient reports a persistent application site reaction (of more than a few days), reports an increase in severity, or reports a skin reaction spreading outside the application site, an assessment of the risks and benefits for the individual patient should be conducted. If a generalized skin reaction associated with the use of Neupro is observed, Neupro should be discontinued.

Melanoma

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear.

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using (Neupro) for *any* indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Magnetic Resonance Imaging and Cardioversion

The backing layer of Neupro contains aluminum. To avoid skin burns, Neupro should be removed prior to magnetic resonance imaging or cardioversion.

Heat Application

The effect of application of heat to the transdermal system has not been studied. However, heat application has been shown to increase absorption several fold with other transdermal products. Patients should be advised to avoid exposing the applied Neupro transdermal system to external sources of direct heat, such as heating pads, or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.

Events Reported with Dopaminergic Therapy

Withdrawal-Emergent-Hyperpyrexia and Confusion

Although not reported with Neupro, a symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, rhabdomyolysis, and/or autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in anti-Parkinsonian therapy. Therefore it is recommended that the dose be tapered at the end of Neupro treatment as a prophylactic measure (See **DOSAGE AND ADMINISTRATION** for guidance on discontinuing Neupro).

Fibrotic complications

Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, pleural thickening, pericarditis and cardiac valvulopathy have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur.

Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, nonergot derived dopamine agonists can cause them is unknown.

Binding to Melanin

As has been reported with other dopamine agonists, binding to melanin-containing tissues (i.e., eyes) in the pigmented rat and monkey was evident after a single dose of rotigotine, but was slowly cleared over the 14-day observation period.

Information for Patients

Patients should be instructed to use Neupro only as prescribed.

Patients should be asked about sensitivity to sulfites. Advise patient that Neupro contains sodium metabisulfite, which may cause allergic-type reactions including anaphylactic symptoms and life threatening or less severe asthmatic episodes in certain susceptible people.

Patients should be alerted to the potential sedating effects associated with Neupro, including somnolence and particularly to the possibility of falling asleep while engaged in activities of daily living. Since somnolence is a frequent adverse event with potentially serious consequences, patients should neither drive a car nor engage in other potentially dangerous activities until they

have gained sufficient experience with Neupro to gauge whether or not it affects their mental and/or motor performance adversely. Patients should be advised that if increased somnolence or new episodes of falling asleep during activities of daily living (e.g., watching television, passenger in a car, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician. If patients have previously experienced somnolence and/or have fallen asleep without warning prior to use of Neupro, they should be advised not to drive, operate machinery, or work at heights during treatment.

As Neupro is administered transdermally, food intake and delayed gastric emptying will not influence the rate of absorption.

Patients should be instructed to wear Neupro continuously for 24 hours. After 24 hours, the patch should be removed and a new one applied immediately. Patients can choose the most convenient time of day or night to apply Neupro but should be advised to apply the patch at approximately the same time each day. If a patient forgets to change a patch, a new patch should be applied as soon as possible and replaced at the usual time the following day.

Neupro should be applied once daily to clean, dry, and intact skin on the abdomen, thigh, hip, flank, shoulder, or upper arm. If applied to a hairy area, the area should be shaved at least 3 days prior to applying the patch. Neupro should not be applied to areas that could be rubbed by tight clothing or under a waistband. Neupro should not be applied to skin folds. Neupro should not be applied to skin that is red, irritated, or impaired. Creams, lotions, ointments, oils, and powders should not be applied to the skin area where Neupro will be placed.

Care should be used to avoid dislodging the patch while showering, bathing or during physical activity. After applying Neupro, patients or caregivers should wash their hands to remove any drug and should be careful not to touch their eyes or any objects. If the edges of the patch lift, Neupro may be taped down with bandage tape. If the patch detaches, a new one may be applied immediately to a different site. The patient should then change the patch according to their regular schedule.

Patients should be informed that application site reactions can occur and that the Neupro transdermal system application site should be rotated on a daily basis (e.g., from the right side to the left side and from the upper body to the lower body). Neupro should not be applied to the same application site more than once every 14 days. If a patient reports a persistent application site reaction (of more than a few days), reports an increase in severity, or reports a skin reaction that spreads outside the application site, an assessment of the risk/benefit balance for the individual patient should be conducted. If a generalized skin reaction associated with the use of Neupro is observed, Neupro should be discontinued.

If there is a skin rash or irritation from the transdermal system, direct sunlight on the area should be avoided until the skin heals. Exposure could lead to changes in the skin color.

Neupro should always be removed slowly and carefully to avoid irritation. After removal the patch should be folded over so that it sticks to itself and should be discarded. After removal the application site should be washed with soap and water to remove any drug or adhesive. Baby or mineral oil may be used to remove any excess residue. Alcohol and other solvents (such as nail polish remover) may cause skin irritation and should not be used. Neupro patients or caregivers should wash their hands to remove any drug and should be careful not to touch their eyes or any objects.

Use of Neupro is associated with nausea, vomiting, and general gastrointestinal distress. Nausea and vomiting may occur more frequently during initial therapy and may require dose adjustment.

Patients should be informed that hallucinations can occur during treatment with Neupro.

Although not reported with Neupro at a greater frequency than with placebo, patients using dopamine agonists may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, syncope, and sweating. Parkinson's disease patients, in addition, appear to have an impaired capacity to respond to a postural challenge and orthostatic hypotension may occur more frequently during initial therapy or with an increase in dose at any time.

Because of the possible additive effects, caution should also be used when patients are taking alcohol, sedating medications, or other CNS depressants (e.g., benzodiazepines, antipsychotics, antidepressants, etc.) in combination with Neupro.

Because applying external heat (e.g., a heating pad, sauna, or hot bath) to the transdermal system may increase the amount of drug absorbed, patients should be instructed not to apply heating pads or other sources of heat to the area of the transdermal system. Direct sun exposure of the transdermal system should be avoided.

Patients should be instructed not to cut or damage Neupro.

To avoid potential burns, Neupro patients should be instructed to remove Neupro before undergoing magnetic resonance imaging (MRI) or cardioversion.

Because of the possibility rotigotine might be excreted in human breast milk, patients should be advised to notify their physicians if they intend to breast-feed or are breast-feeding an infant.

Because experience in humans is limited, patients should be advised to notify their physician if they become or plan to become pregnant during therapy. (See **PRECAUTIONS, Pregnancy)**

There have been reports of patients experiencing intense urges to gamble, increased sexual urges, and other intense urges while taking one or more of the medications generally used for the treatment of Parkinson's disease, including Neupro. Although it is not proven that the medications caused these events, these urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped. Prescribers should ask patients about the development of new or increased gambling urges, sexual urges or other urges while being treated with Neupro. Patients should inform their physician if they experience new or increased gambling urges, increased sexual urges or other intense urges while taking Neupro. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking Neupro.

Drug Interactions

CYP Interactions

In vitro studies indicate that multiple CYP-isoforms are capable of catalyzing the metabolism of rotigotine. In human liver microsomes, no extensive inhibition of the metabolism of rotigotine was observed when co-incubated with CYP isoform specific inhibitors. If an individual CYP isoform is inhibited, other isoforms can catalyze rotigotine metabolism.

Rotigotine, the 5-O-glucuronide and its desalkyl and monohydroxy metabolites were analyzed for interactions with the human CYP isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 *in vitro*. Based on these results, no risk for inhibition of CYP1A2, CYP2C9 and

CYP3A4 catalyzed metabolism of other drugs is predicted at therapeutic rotigotine concentrations. There is a low risk of inhibition of CYP2C19 and CYP2D6 catalyzed metabolism of other drugs at therapeutic concentrations.

In human hepatocytes in vitro, there was no indication for induction of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4.

Rotigotine is metabolized by multiple sulfotransferases and two UDP-glucuronosyltransferases (UGT1A9 and UGT2B15). These multiple pathways make it unlikely that inhibition of any one pathway would alter rotigotine concentrations significantly.

Protein Displacement, Warfarin

In vitro, no potential for displacement of warfarin by rotigotine (and vice versa) from their respective human serum albumin binding sites was detected.

Digoxin

The effect of rotigotine t on the pharmacokinetics of digoxin has been investigated *in vitro* in Caco-2 cells. Rotigotine did not influence the P-glycoprotein-mediated transport of digoxin. Therefore, rotigotine would not be expected to affect the pharmacokinetics of digoxin.

Cimetidine

Co-administration of rotigotine (up to 4 mg/24 hours) with cimetidine (400 mg b.i.d.), an inhibitor of CYP1A2, CYP2C19, CYP2D6, and CYP3A4, did not alter the steady-state pharmacokinetics of rotigotine in healthy subjects.

L-dopa

Co-administration of L-dopa/carbidopa (100/25mg b.i.d.) with rotigotine (4 mg/24 hours) had no effect on the steady-state pharmacokinetics of rotigotine; rotigotine had no effect on the pharmacokinetics of L-dopa/carbidopa.

Dopamine Antagonists

It is possible that dopamine antagonists, such as antipsychotics or metoclopramide, could diminish the effectiveness of rotigotine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year subcutaneous carcinogenicity studies of rotigotine were conducted in CD-1 mice at doses of 0, 3, 10 and 30 mg/kg and in Sprague-Dawley rats at doses of 0, 0.3, 1, and 3 mg/kg; in both studies rotigotine was administered once every 48 hours. No significant increases in tumors occurred in the mouse study at doses up to 12 times the maximum recommended human dose (MRHD) of 6 mg/24 hours.

In rats, there were significant increases in Leydig cell tumors in males and uterine tumors (adenocarcinomas, squamous cell carcinomas) in females. These findings are of questionable significance because the endocrine mechanisms believed to be involved in the production of Leydig cell and uterine tumors in rats are not considered relevant to humans. Therefore, there were no significant tumor findings considered relevant to humans at plasma exposures (AUC) up to 5 to 9 times the plasma AUC in humans at the MRHD.

Mutagenesis

Rotigotine was not mutagenic in the *in vitro* Ames test or the *in vivo* Unscheduled DNA Synthesis test in hepatocytes from male Fisher rats. In the *in vitro* mouse lymphoma assay, rotigotine was mutagenic and clastogenic in the presence and absence of metabolic activation. Rotigotine was not clastogenic in the in vivo mouse micronucleus test.

Infertility

When administered to female Sprague-Dawley rats prior to and during mating and through gestation day 7, rotigotine disrupted implantation at subcutaneous (s.c.) doses of 1.5 mg/kg/day (2 times the maximum recommended human dose (MRHD) on a mg/m^2 basis) or greater. There was no no-effect dose. In male rats treated from 70 days prior to and through mating, there was no effect on fertility; however, a decrease in epididymal sperm motility was observed at 15 mg/kg. The no-effect dose was 5 mg/kg/day (8 times the MRHD on a mg/m^2 basis). Rotigotine was administered to female CD-1 mice at s.c. doses of 10, 30, and 90 mg/kg/day (8 to 73 times the MRHD on a mg/m^2 basis) from 2 weeks until 4 days before mating and then at a dose of 6 mg/kg/day (all groups) (5 times the MRHD on a mg/m^2 basis) from 3 days before mating until gestation day 7; disrupted implantation was observed at all doses. The effects on implantation are thought to be due to the prolactin-lowering effect of rotigotine. In humans, chorionic gonadotropin, not prolactin, is essential for implantation.

Pregnancy

Pregnancy Category C

In subcutaneous studies in Sprague-Dawley rats and CD-1 mice, rotigotine was shown to have adverse effects on embryo-fetal development. Rotigotine given to pregnant rats during organogenesis (0.5, 1.5 or 5 mg/kg/day on gestation days 6 through 17) resulted in increased fetal death at all doses. The lowest effect dose was 0.8 times the MRHD on a mg/m^2 basis. This effect is thought to be due to the prolactin-lowering effect of rotigotine. Rotigotine given to pregnant mice during organogenesis (10, 30 or 90 mg/kg/day on gestation days 6 through 15) resulted in an increased incidence of skeletal retardation at 30 and 90 mg/kg/day, and an increase in fetal death at 90 mg/kg/day. No effects were observed at 10 mg/kg/day (8 times the MRHD on a mg/m^2 basis). Rotigotine given to pregnant Himalayan rabbits during organogenesis (1, 5, or 15 mg/kg/day (3-49 times the MRHD on a mg/m^2 basis) on gestation days 6 through 20) had no effects on embryo-fetal development; however, the study was not conducted at sufficiently high doses. In a pre- and postnatal development study, Sprague-Dawley rats were administered 0.1, 0.3 or 1 mg/kg/day from gestation day 6 through postnatal day 21. Rotigotine impaired growth and development of offspring during lactation and produced neurobehavioral abnormalities in offspring at 1 mg/kg/day. When offspring were mated, growth and survival of their offspring were adversely affected. No adverse effects were observed at 0.3 mg/kg/day (0.5 times the maximum recommended human dose on a mg/m^2 basis).

There are no adequate and well-controlled studies using Neupro in pregnant women.

Therefore, the use of Neupro cannot be recommended during pregnancy unless the potential benefits of therapy justify the potential risk to the fetus.

Nursing Mothers

Rotigotine decreases prolactin secretion in humans and could potentially inhibit lactation.

Studies in rats have shown that rotigotine and/or its metabolite(s) is excreted in breast milk. It is not known whether rotigotine is excreted in human breast milk. Because of the possibility that rotigotine may be excreted in human milk, and because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use

Safety and effectiveness in pediatric patients have not been established.

Geriatric use

Of the subjects treated with Neupro in clinical studies for treatment of early-stage Parkinson's disease, 42% were 65 years old and over, and 9% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

No overall differences in plasma levels of rotigotine were observed between patients who were 65 to 80 years old compared with younger patients receiving the same rotigotine doses. (See **CLINICAL PHARMACOLOGY, Geriatric Patients)**

ADVERSE REACTIONS

The safety of Neupro was evaluated in a total of 649 patients who participated in three double-blind, placebo-controlled studies with durations of 3 to 9 months in patients with early-stage Parkinson's disease. Additional safety information was collected in earlier short term studies, and two open-label extension studies in patients with early-stage Parkinson's Disease.

In the 3 double-blind, placebo-controlled studies in patients with early-stage Parkinson's disease, the most commonly observed AEs (incidence ≥5%) that appeared substantially more frequently in the rotigotine groups than in the placebo groups were nausea, application site reaction, somnolence, dizziness, headache, vomiting, and insomnia.

Approximately 13% of 649 rotigotine-treated patients who participated in the 3 longest controlled studies discontinued treatment because of AEs, compared with 6% of 289 patients who received placebo. The adverse events most commonly causing discontinuation of treatment were: application site reaction (5% vs 0% on placebo), nausea (2% vs 0% on placebo), and vomiting (1% vs 0% on placebo).

Adverse Events Incidence in Controlled Clinical Studies in Early-Stage Parkinson's Disease

Table 5 lists treatment-emergent adverse events that occurred in the three placebo-controlled studies in early-stage Parkinson's disease in ≥2% of the patients treated with Neupro and were more frequent than in the placebo group. In these studies, patients did not receive concomitant L-dopa.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse reactions in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies

cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and no-drug factors to the adverse-events incidence rate in the population studied.

Table 5 Treatment-Emergent Adverse Event (Regardless of Causal Relationship) Incidence in Double-Blind, Placebo-Controlled Early-Stage Parkinson's Disease Studies (Events ≥2% of Subjects Treated with Neupro and Numerically More Frequent Than in the Placebo Group)

Body system/preferred term	Placebo N=289 (%)	Neupro N=649 (%)
Application site reactions	14	37
Autonomic nervous system		
Sweating increased	2	4
Mouth dry	1	3
Body as a Whole		
Fatigue	7	8
Accident NOS	4	5
Cardiovascular		
Extremity edema	6	7
Hypertension	2	3
Central and peripheral nervous system		
Dizziness	11	18
Headache	10	14
Vertigo	2	3
Gastrointestinal system		
Nausea	15	38
Vomiting	2	13
Constipation	4	5
Dyspepsia	1	4
Anorexia	1	3
Musculoskeletal system		
Back pain	5	6
Arthralgia	3	4
Psychiatric		
Somnolence	16	25
Insomnia	5	10

Body system/preferred term	Placebo N=289 (%)	Neupro N=649 (%)
Dreaming abnormal	<1	3
Hallucination	1	2
Respiratory system - Sinusitis	2	3
Skin and appendage – erythematous rash	1	2
Urinary tract infection	1	3
Vision abnormal	1	3

671 NOS=not otherwise specified

672 Other AEs reported by more than 2% of patients with early-stage Parkinson's disease treated
673 with rotigotine (as displayed), but that were equally or more frequent in the placebo group (after
674 rounding) were: asthenia, influenza-like symptoms, diarrhea, depression, rhinitis, micturition
675 frequency, upper respiratory tract infection, fall, tremor, coughing, anxiety, abdominal pain, and
676 chest pain.

677 The incidence of AEs was not materially different between men and women in the pooled studies
678 presented in Table 5.

679 Dose-Related Adverse Events

680 Many AEs appeared to be dose-related . Table 6 illustrates AEs that were dose-related based
681 upon the highest frequency of AEs occurring with the 6 mg/24 hours dose or with the 4 and 6
682 mg/24 hours doses compared to the frequency for placebo and the 2 mg/24 hours dose. Rates for
683 the non-recommended 8 mg/24 hr. dose are also shown. Some AEs (anorexia; constipation;
684 vision abnormal) were found to be dose-related only when their onset was in the titration period.
685 Dizziness was only dose-related when it had its onset in the maintenance period.

686

687

688 **Table 6 Incidence (%) of Neupro Dose-Related Treatment-Emergent Adverse Events**
689 **During the Whole Study Period in the Dose-Response Study**

Preferred Term Adverse Event	Placebo N = 64	Daily Neupro Dose			
		2 mg/24 hours N = 67	4 mg/24 hours N = 63	6 mg/24 hours N = 65	8 mg/24 hours N = 70
Application site reaction	19	24	21	34	46
Nausea	11	34	38	48	41
Vomiting	3	10	16	20	11
Weight decrease	0	0	0	2	3
Myalgia	0	0	2	2	3
Somnolence	3	13	16	19	21
Insomnia	8	6	13	14	14

Dreaming abnormal	0	2	5	3	7
Hallucination	2	0	2	3	3
Rash erythematous	2	2	6	3	3

690

691

692 Laboratory changes

693 Subjects who received Neupro experienced an average decline in blood hemoglobin levels of
694 about 2% or 0.3 g/dL relative to subjects who received placebo. A decline in blood hemoglobin
695 from baseline of 2 g/dL or more was seen in 4% with Neupro and 1% with placebo. Among
696 subjects with normal baseline hemoglobin levels, about 8% of those who received Neupro
697 developed low hemoglobin levels compared to 5% with placebo. Subjects receiving Neupro who
698 experienced declines in blood hemoglobin were also noted to have declines in serum albumin. It
699 is not known whether these changes are readily reversible with discontinuation of Neupro.

700 Subjects who received Neupro also experienced an average increase in blood urea nitrogen
701 (BUN) levels of about 3.7% or 0.21 mg/dL relative to subjects who received placebo. There was
702 also a higher incidence of abnormally elevated levels of BUN associated with treatment. There
703 were no significant differences between Neupro and placebo in levels of serum creatinine. It is
704 not known whether these changes are readily reversible with discontinuation of Neupro or
705 whether they represent changes in renal function.

706 Treatment with Neupro was associated with a greater likelihood of low levels of blood glucose
707 (less than 50 mg/dL). Among subjects with normal baseline glucose levels, about 7% of subjects
708 who received Neupro developed at least one low blood glucose level compared to 4% with
709 placebo.

710 **Other Adverse Reactions Observed in Subjects with Early-Stage Parkinson's**
711 **Disease during Phase 2 and 3 Studies**

712 Rotigotine was administered to 1220 subjects with early-stage Parkinson's disease in Phase 2
713 and 3 clinical studies, including 6 double-blind, placebo-controlled studies; 319 were in an open-
714 label study in patients with early-stage Parkinson's disease. Adverse events occurring in
715 rotigotine treated patients at least twice, or if the AE was serious, at least once, and events not
716 described elsewhere in labeling, are provided in the following listing. Events too poorly
717 described or not plausibly related to treatment were also omitted. Events are further classified
718 within body system categories and enumerated in order of decreasing frequency using the
719 following definitions: frequent AEs are defined as those occurring in at least 1/100 patients;
720 infrequent AEs are those occurring in 1/100 to 1/1000 patients; and rare events are those
721 occurring in fewer than 1/1000 patients.

722 **Application site disorders:** *frequent* –contact dermatitis

723 **Autonomic nervous system:** *infrequent* – saliva increased, appetite increased, impotence,
724 flushing

725 **Body as a whole:** *frequent* –leg pain, malaise, fever; *infrequent* – allergic reaction, rigors, hot
726 flushes, hyperesthesia

727 **Cardiovascular disorders, general:** *frequent* –syncope; *infrequent* –cardiac failure

Central and peripheral nervous system disorders: *frequent* – paresthesia, confusion, ataxia, gait abnormal, neuralgia, hypoesthesia, hypertonia; *rare*-convulsions

Hearing and vestibular disorders: *infrequent* – tinnitus

Heart rate and rhythm disorders: *infrequent* –, AV (atrioventricular) block, bundle branch block, fibrillation atrial; *rare* – arrhythmia ventricular, tachycardia ventricular

Hematologic disorders: *infrequent* – thrombocytopenia

Liver and biliary disorders: *frequent* – GGT (gamma-glutamyl transferase) increased

Metabolic and nutritional disorders: *frequent* – weight increase

Psychiatric disorders: *infrequent* –paranoid reaction, psychosis

Skin and appendage disorders: *frequent* –pruritus

Urinary system disorders: *frequent* – urinary incontinence

Vascular disorders: *frequent* – purpura

Vision disorders: *infrequent* – photopsia

OVERDOSAGE

There were no reports of overdose of Neupro in the clinical studies.

Since Neupro is a transdermal system, overdosing is not likely to occur in clinical practice unless patients forget to remove the previous day's transdermal system; patients should be warned against this possibility.

Overdose Management

There is no known antidote for overdosage of dopamine agonists. In case of suspected overdose, the transdermal system(s) should immediately be removed from the patient. Concentrations of rotigotine decrease after patch removal. The terminal half-life of rotigotine is 5 to 7 hours. If it is necessary to discontinue use of rotigotine after overdose, it should be discontinued gradually to prevent neuroleptic malignant syndrome. (See **PRECAUTIONS**) The daily dose should be reduced by 2 mg/24 hours with a dose reduction preferably every other day, until complete withdrawal of rotigotine is achieved. Before completely stopping use of Neupro in the event of an overdose, please consult the **DOSAGE AND ADMINISTRATION** section.

The predominant symptoms of overdose with Neupro are expected to be nausea, vomiting, hypotension, involuntary movements, hallucinations, confusion, convulsions, and other signs of excessive dopaminergic stimulation.

The patient should be monitored closely, including heart rate, heart rhythm, and blood pressure. As shown in a study of renally impaired patients, dialysis is not expected to be beneficial. Treatment of overdose may require general supportive measures to maintain vital signs.

DOSAGE AND ADMINISTRATION

Initiation of Therapy

Neupro should be started at 2 mg/24 hours. Based upon individual patient clinical response and tolerability, Neupro dosage may be increased weekly by 2 mg/24 hours if tolerated and if additional therapeutic effect is needed. The lowest effective dose was 4 mg/24 hours. The

highest recommended dose is 6 mg/24 hours. Doses above 6 mg/24 hours have not shown any additional therapeutic benefit (See **CLINICAL STUDIES**, Dose-Response Study) and are associated with an increased incidence of adverse reactions (see Adverse Reactions) If it is necessary to discontinue use of Neupro, it should be discontinued gradually. The daily dose should be reduced by 2 mg/24 hours with a dose reduction preferably every other day, until complete withdrawal of Neupro. (see Precautions; Withdrawal-Emergent-Hyperpyrexia and Confusion)

Administration of transdermal system

Neupro is applied once-a-day. The adhesive side of the transdermal system should be applied to clean, dry, intact healthy skin on the front of the abdomen, thigh, hip, flank, shoulder, or upper arm. The transdermal system should be applied at approximately the same time every day, at a convenient time for the patient. Because Neupro is administered transdermally, food is not expected to affect absorption and it can be applied irrespective of the timing of meals. No dosage adjustment is necessary for patients who have moderate impairment of hepatic function or mild to severe impairment of renal function.

The application site for Neupro should be moved on a daily basis (for example, from the right side to the left side and from the upper body to the lower body). Neupro should not be applied to the same application site more than once every 14 days and should not be placed on skin that is oily, irritated, or damaged, or where it will be rubbed by tight clothing. If it is necessary to apply Neupro to a hairy area, the area should be shaved at least 3 days prior to Neupro application. The system should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place for 20 to 30 seconds, making sure there is good contact, especially around the edges. If the patient forgets to replace Neupro, or if the transdermal system becomes dislodged, another transdermal system should be applied for the remainder of the day.

Complete instructions to facilitate patient counseling on proper usage may be found in the **PRECAUTIONS, Information for Patients** section and in the **PATIENT INFORMATION LEAFLET.**

Animal Toxicology

Retinal Pathology: Albino rats: Retinal degeneration was observed in albino rats in the 6-month toxicity study at the highest dose tested. Retinal degeneration was not observed in the 2-year carcinogenicity studies in albino rat (at plasma exposures (AUC) up to 5 to 9 times the plasma AUC in humans at the MRHD of 6 mg/24 hours) and albino mouse, or in monkeys treated for 1 year. The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (i.e., disk shedding) may be involved.

HOW SUPPLIED

Neupro® is available in 3 strengths, as described in Table 7:

Table 7 Transdermal System Size, Drug Content, and Nominal Delivery Rate

Neupro Nominal Dose	Rotigotine Content per System	Neupro System Size
2 mg/24 hours	4.5 mg	10 cm^2
4 mg/24 hours	9 mg	20 cm^2
6 mg/24 hours	13.5 mg	30 cm^2

Each transdermal system is packaged in a separate pouch.

Each strength is available in cartons of 7 and 30 transdermal systems.

2 mg/24 hours 7 transdermal systems	NDC # 0091-6486-21
2 mg/24 hours 30 transdermal systems	NDC # 0091-6486-01
4 mg/24 hours 7 transdermal systems	NDC # 0091-6487-21
4 mg/24 hours 30 transdermal systems	NDC # 0091-6487-01
6 mg/24 hours 7 transdermal systems	NDC # 0091-6488-21
6 mg/24 hours 30 transdermal systems	NDC # 0091-6488-01

Storage

Store at 20° - 25°C (68° - 77°F); excursions permitted between 15° - 30°C (59° - 86°F). [See USP Controlled Room Temperature]

Neupro should be stored in the original pouch. Do not store outside of pouch.

Apply the transdermal system immediately upon removal from the pouch.

Manufactured for:
SCHWARZ PHARMA, LLC
Mequon, WI 53092, USA

By:
LTS Lohmann Therapie System AG
Lohmannstrasse 2
D-56626 Andernach, Germany

PC4862
Rev. 07/04

PATIENT INFORMATION
NEUPRO® [NU pro]
(rotigotine transdermal system)

Rx Only

IMPORTANT: NEUPRO is for use on the skin only.

Read the Patient Information that comes with NEUPRO before you start using it and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment. If you have any questions about NEUPRO, ask your doctor or pharmacist.

What is the most important information I should know about NEUPRO?

NEUPRO may make you very sleepy or cause you to fall asleep suddenly, and without warning while doing normal activities such as driving, talking with other people, watching TV, or eating. This can happen any time during treatment with NEUPRO.

- Do not drive, work on ladders, or do other dangerous activities while using NEUPRO until you know how NEUPRO affects you.
- If NEUPRO does make you very sleepy, or you fall asleep suddenly while doing normal activities, do not drive or do other dangerous activities until you talk with your doctor.

Tell your doctor if you fall asleep suddenly while doing normal activities or feel sleepier than normal.

Heat may cause too much medicine from a Neupro patch to pass through your skin. While you are wearing a NEUPRO patch, do not:

- **apply a heating pad to the application site area**
- **take a hot bath**
- **use a sauna**
- **expose the application site to direct sunlight**

What is NEUPRO?

NEUPRO is a type of medicine called a dopamine agonist. NEUPRO is a patch (transdermal delivery system) worn on the skin. It is used to treat the signs and symptoms of early-stage Parkinson's disease in adults.
NEUPRO has not been studied in children.

Who should not use NEUPRO?

Do not use NEUPRO if you are allergic to anything in it. See the end of this leaflet for a complete list of ingredients in NEUPRO.

NEUPRO contains a sulfite called sodium metabisulfate. Sulfites can cause life-threatening allergic reactions in people that are sensitive to sulfites. People with asthma are more likely to be sensitive to sulfites. If you have trouble breathing or swallowing while using NEUPRO, remove NEUPRO right away and call your doctor or get emergency care.

NEUPRO may not be right for you. Before starting NEUPRO tell your doctor about all of your health conditions including if you:

- are allergic to sulfites
- have asthma
- have blood pressure problems
- have heart problems
- are pregnant or breastfeeding or planning on becoming pregnant

Tell your doctor if you drink alcohol
Alcohol should be avoided while using NEUPRO. ALCOHOL and NEUPRO can interact and increase your chance of being sleepy or falling asleep suddenly while doing normal activities.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Some medicines may affect how NEUPRO works. NEUPRO may also affect how your other medicines work. **Especially tell your doctor if you take other medicines that can make you sleepy such as sleep medicines, antidepressants, or antipsychotics.**

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I use NEUPRO?

See the end of this leaflet for complete instructions "How to use and apply a NEUPRO patch."

- Use NEUPRO exactly as prescribed by your doctor.
- NEUPRO comes in 4 different size (dose) patches. Your doctor will probably start you on a low dose of NEUPRO. Your doctor will change the dose weekly until you are taking the right amount of medicine to control your symptoms. It may take several weeks before you reach the dose that controls your symptoms best. Do not stop or change your dose of NEUPRO without first talking with your doctor.
- Talk to your doctor often about your condition. **Do not stop or change your treatment with Neupro without talking to your doctor.**
- **Patients with Parkinson's disease may have an increased chance of getting a skin cancer called melanoma. People with Parkinson's disease should have a doctor check their skin for skin cancer regularly.**

What are the possible side effects of NEUPRO?

Possible serious side effects with NEUPRO include:

- **falling asleep while do normal activities.** See "What is the most important information I should know about NEUPRO?"
- **low blood pressure** that makes you feel dizzy, faint, sweaty, or have nausea. Stand up slowly when getting up from a sitting or lying position. Tell you doctor if you if you have symptoms of low blood pressure with NEUPRO.
- **fainting**
- **hallucinations** (seeing, hearing, or sensing things that are not real). The chance for hallucinations is higher in elderly patients with Parkinson's disease.
- **compulsive** behavior and trouble controlling strong urges such as:
  - gambling too much
  - increased sexual desire
  - repeating meaningless actions

Talk to your doctor if you or family members notice that you are having unusual urges

-

The most common side effects with NEUPRO are:

- nausea
- application site reaction
- drowsiness or sleepiness
- dizziness
- headache
- vomiting
- trouble sleeping (insomnia)

These are not all the side effects of NEUPRO. For more information, ask your doctor or pharmacist. Talk to your doctor about any side effects or problems you may have.

How do I store NEUPRO?

- Store NEUPRO at 68° to 77°F (20° to 25°C).
- Store NEUPRO in its sealed pouch until use.
- **Keep NEUPRO and all medicines out of reach of children and away from pets.**

General information about NEUPRO

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use NEUPRO for a condition for which it was not prescribed. Do not give NEUPRO to other people even if they have the same condition you have. It may harm them.

This leaflet summarizes important information about NEUPRO. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about NEUPRO that was written for healthcare professionals.

For more information, visit www.website.com or call 1-800-xxx-xxxx.

What are the ingredients in NEUPRO?

Active ingredient: rotigotine

Inactive ingredients: ascorbyl palmitate, povidone, silicone adhesive, sodium metabisulfite, and dl-alpha-tocopherol.

How to use and apply a NEUPRO patch

Read these instructions carefully before you apply NEUPRO. Ask your doctor or pharmacist about anything you do not understand.

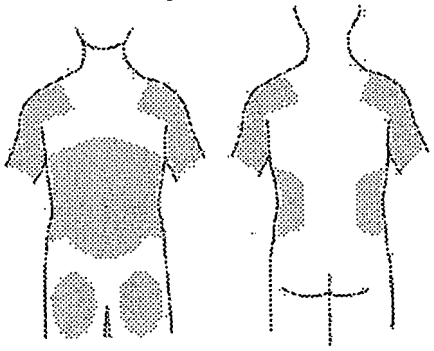
When to Apply NEUPRO:

Each patch is sealed in a pouch that protects it until you are ready to apply it.

- NEUPRO should be applied right away after removing it from the protective pouch.
- Wear NEUPRO for 24 hours. After 24 hours, remove the patch and apply a new one right away to a different area of skin.
- Choose the time of day or night that works best for you to apply NEUPRO. Apply the patch at the same time each day.

Where to Apply NEUPRO:

- Choose an area of clean, dry, and healthy skin on the stomach, thigh, hip, flank (side of the body between the ribs and the pelvis), shoulder, or upper arm.



- If you need to apply the patch to a hairy area, the area should be shaved at least 3 days before applying the patch.
- The patch should not be applied to areas where it could be rubbed by tight clothing or under a waistband.
- Avoid applying the patch on skin folds.
- Do not apply the patch to skin that is red, irritated, or injured.
- Each patch should be applied to a different place on the skin each day, for example, from the right side to the left side and from the upper body to the lower body.

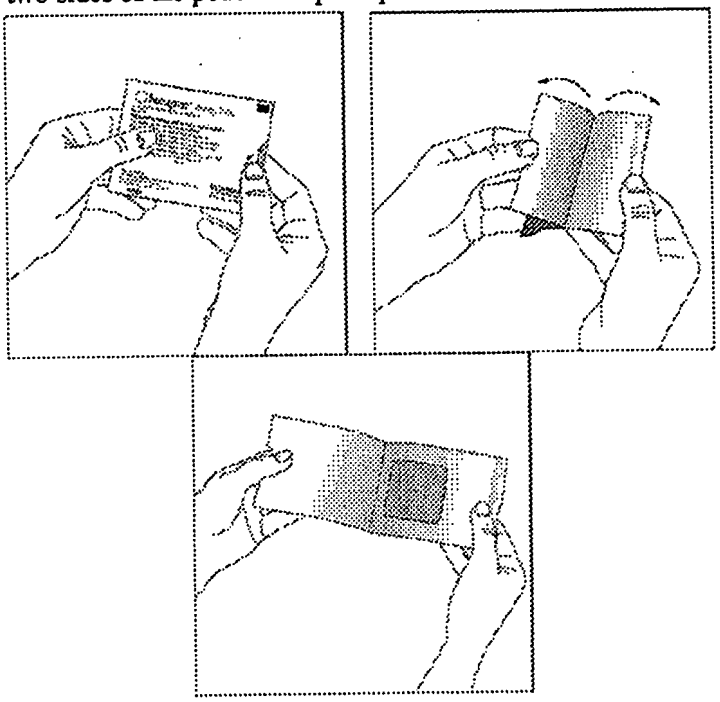
NEUPRO should not be applied to the same area of skin more than once every 14 days.

- Creams, lotions, ointments, oils, and powders should not be applied to the skin area where the patch will be placed.

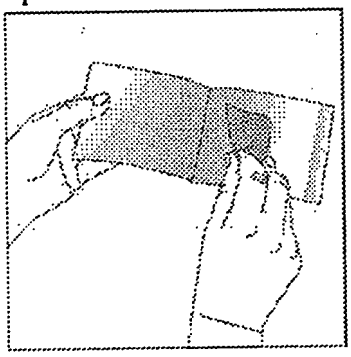
How to Apply NEUPRO:

Each patch is individually packaged. Just before you apply the patch, remove it from its sealed pouch, remove the protective liner and apply to the skin right away. Do not store the patch outside the sealed pouch. Do not cut a NEUPRO patch into smaller pieces.

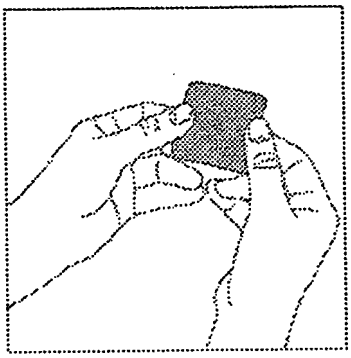
1. Grasp the two sides of the pouch and pull apart.



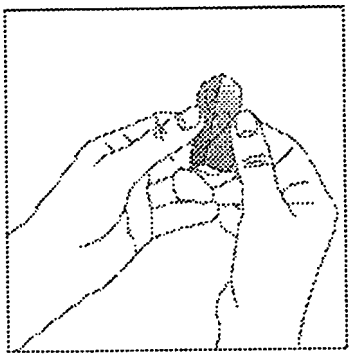
2. Remove the patch from the pouch.



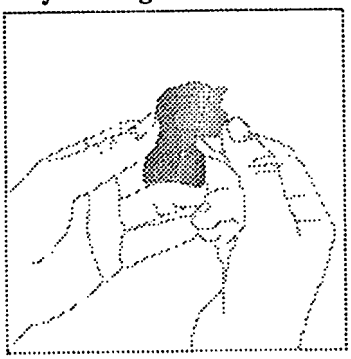
3. Hold the patch with both hands, with the protective liner on top.



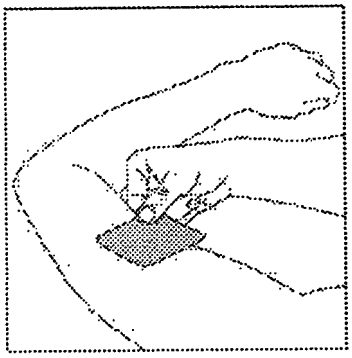
4. Bend the edges of the patch away from you so that the S-shaped cut in the liner opens up.

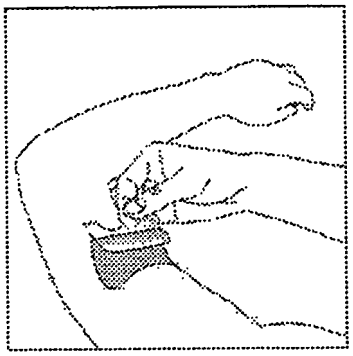


5. Peel off one half of the protective liner. **Do not touch the sticky surface because the medicine could come off on your fingers.**

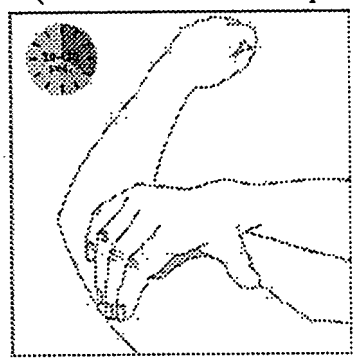


6. Apply the sticky half of the patch to a clean area of skin and remove the remaining liner.





7. Press the patch firmly with the palm of your hand for **20 to 30** seconds to make sure there is good contact with the skin, especially around the edges. Make sure that the patch is flat against the skin (there should be no bumps or fold in the patch).



8. Be sure to wash your hands with soap and water right after handling the patch to remove any medicine that may have gotten on them. Do not touch your eyes until after you have washed your hands.

How to Remove NEUPRO:

1. Slowly and carefully peel off the used patch. Carefully fold it in half (sticky sides together) and throw away the folded patch so that children and pets cannot reach it. This patch still contains some medicine and could harm a child or pet.
2. Gently wash the area with warm water and mild soap to remove any sticky material (adhesive) that stays on your skin. Baby or mineral oil may also be used to remove any adhesive. Alcohol or other solvents, such as nail polish remover, may cause skin irritation and should not be used.
3. Wash your hands with soap and water.
4. You may see mild redness at the site when a patch is removed. This redness should go away over time. If irritation or itchiness continues, tell your doctor.

Other Information:

- Heat may cause too much medicine from a Neupro patch to pass through your skin. While you are wearing a NEUPRO patch, do not:
  - apply a heating pad to the application site area
  - take a hot bath

  - use a sauna
  - expose the application site to direct sunlight
- You may bathe, shower, or swim while wearing a NEUPRO patch. Water may loosen your NEUPRO patch. If a NEUPRO patch falls off, apply a new NEUPRO patch for the rest of the day. The following day, apply a new patch at your regular time.
- If you forget to apply a NEUPRO patch at the usual time, remove the used NEUPRO patch you are currently wearing and put on a new NEUPRO patch on a different area of skin. Then apply a new NEUPRO patch the next day at your regular time.
- If you develop a skin rash or irritation from the patch, avoid direct sunlight on the area until the skin heals because sun exposure could lead to changes of skin color.
- Do not cut or damage a NEUPRO patch.
- To avoid a possible burn on your skin, remove your NEUPRO patch before you have procedures called magnetic resonance imaging (MRI) or a cardioversion.

Distributed by:

SCHWARZ PHARMA, LLC
Mequon, WI 53092

PC4803
Rev. 06/06

EXHIBIT F

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-829

Schwarz BioSciences, Inc.
Attention: David Dobrowski
Director, Regulatory Affairs
P.O. Box 110167
Research Triangle Park, NC 27709

Dear Mr. Dobrowski:

Please refer to your new drug application (NDA) dated January 19, 2005, received January 28, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act submitted under 505(b) for Neupro (rotigotine) 2mg/24 hr., 4 mg/24 hr., and 6 mg/24hr.transdermal system.

We acknowledge receipt of your submissions dated:

February 23, 2006	March 16, 2006	April 24, 2006
August 25, 2006	August 31, 2006	October 2, 2006
November 7, 2006	December 7, 2006	January 10, 2007
January 24, 2007	February 5, 2007	April 4, 2007
May 4, 2007	May 8, 2007	

The November 7, 2006 submission constituted a complete response to our February 28, 2006 action letter.

This new drug application provides for the use of Neupro (rotigotine) transdermal system for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease.

We have completed our review of this application, as amended and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled Providing *Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these

submissions "**FPL for approved NDA 21-829.**" Approval of these submissions by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

We remind you of your postmarketing study commitments in your submission dated May 4, 2007. These commitments are listed below.

1. Description of Commitment

   To complete your thorough QTc study characterizing the effects of rotigotine on cardiac repolarization in humans and submit the final study report.

Protocol Submission:	to IND 47,852 on December 13, 2005
Study Start:	by January 6, 2006
Final Report Submission:	by July 31, 2007

2. Description of Commitment

   To complete the echocardiographic study in patients with Parkinson's disease comparing the effects of different dopamine agonists, including rotigotine, on echocardiographic measures. This study will help determine if rotigotine is associated with the cardiac valvulopathy seen with some other dopamine agonists.

Protocol Submission:	by June 30, 2007
Study Start:	by April 2007
Interim Report Submission:	September 2009
Final Report Submission:	September 2011

3. Description of Commitment

   To complete a fixed-dose dose-response study of rotigotine in patients with advanced Parkinson's disease that incorporates monitoring of laboratory parameters related primarily to hematopoesis and renal function, including iron, transferrin, ferritin, reticulocyte count, red cell morphology, erythropoietin, erythrocyte sedimentation rate, C-reactive protein, haptoglobin and urine hemoglobin as well as hemoglobin; hematocrit; red cell indices; absolute and differential white cell counts; BUN, creatinine, serum electrolytes (including bicarbonate), albumin and globulin. This study will include continued detailed monitoring during post-treatment washout in order to assess rate of recovery from any reduction of renal function, hemoglobin or albumin. Measurement of red cell volume and creatinine clearance should be performed before initiating treatment, at the end of treatment and the end of post-treatment washout. These data will help to further characterize the previously noted changes in hematologic and renal measures and, importantly, to determine if, in those patients in whom these changes occur, the changes are reversible upon discontinuation of treatment.

Protocol Submission:	by June 30, 2007
Study Start:	by August 2007
Final Report Submission:	by February 2010

4. Description of Commitment

To conduct an in vivo micronucleus assay by the subcutaneous route.

Protocol Submission:	to NDA 21-829 on August 25, 2006
Study Start:	by September 2006
Final Report Submission:	by June 30, 2007

5. Description of Commitment

To conduct embryo-fetal development studies in mouse.

Protocol Submission:	to NDA 21-829 on August 25, 2006
Study Start:	by October 2006
Final Report Submission:	by September 30, 2007

6. Description of Commitment

To conduct an embryo-fetal development study in rabbit.

Protocol Submission:	to NDA 21-829 on August 25, 2006
Study Start:	by October 2006
Final Report Submission:	by September 30, 2007

7. Description of Commitment

To conduct a local tissue distribution study to compare tissue distribution of drug-related material at the site of application following subcutaneous and dermal administration.

Protocol Submission:	by June 30, 2007
Study Start:	by August 2007
Final Report Submission:	by December 31, 2007

If local tissue exposure to drug-related material following subcutaneous administration (route used in the completed 2-year carcinogenicity studies) is not essentially the same as that following dermal administration, then a 2-year dermal carcinogenicity study in one species will be conducted.

Protocol Submission:	by March 2008
Study Start:	by May 2008
Final Report Submission:	by September 30, 2011

8. Description of Commitment
To conduct an in vitro binding assay to assess the affinity of the metabolite, rotigotine sulfate, at the serotonin $5HT_{2B}$ receptor.

Protocol Submission:	by July 2007
Study Start:	by September 2007
Final Report Submission:	by February 28, 2008

Additional Nonclinical Comments

1. You have provided protocols for the embryo-fetal development studies in mouse and rabbit that are to be conducted Phase 4. The study protocols describe standard embryo-fetal studies; however, concurrence cannot be provided on dose selection since no dose-range finding data were provided. Doses should be selected based on data from valid dose-ranging studies in each species, preferably collected by the laboratory conducting the pivotal studies. In each pivotal study, rotigotine should be tested at doses up to a clear maximum tolerated (or maximum feasible) dose.

2. If a 2-year carcinogenicity is conducted Phase 4, it is recommended that the study be conducted using a clinical formulation containing the hydroxylamine degradant at or above the proposed limit (188 ppm) in order to provide additional assurance of safety.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence.**"

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Neurology Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call CDR Teresa Wheelous, Sr. Regulatory Project Manager, at (301) 796-1161.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Office Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Package Insert and Patient Package Insert

Neupro®

(Rotigotine Transdermal System)

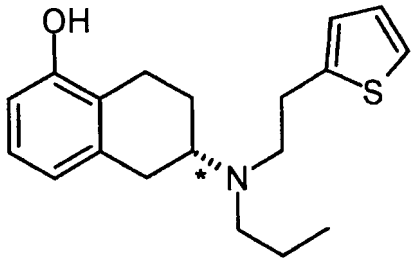
CONTINUOUS DELIVERY FOR ONCE-DAILY APPLICATION

Rx Only

DESCRIPTION

Neupro® (Rotigotine Transdermal System) is a transdermal delivery system that provides rotigotine, a non-ergolinic dopamine agonist. When applied to intact skin, Neupro is designed to continuously deliver rotigotine over a 24-hour period.

The chemical name of rotigotine is (6S)-6-{propyl[2-(2-thienyl)ethyl]amino}-5,6,7,8-tetrahydro-1-naphthalenol. The empirical formula is $C_{19}H_{25}NOS$. The molecular weight is 315.48. The structural formula for rotigotine is:



The asterisk designates the chiral center.

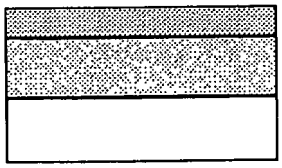
Neupro is available in three strengths: 2, 4, and 6 mg/24 hours. Each transdermal system has a release surface area of 10, 20, and 30 cm^2 and contains 4.5, 9, or 13.5 mg rotigotine, respectively. See Table 1. The composition of the transdermal system per area unit is identical.

Table 1 Transdermal System Size, Drug Content, and Nominal Delivery Rate

Neupro Nominal Dose	Rotigotine Content per System	Neupro System Size
2 mg/24 hours	4.5 mg	10 cm^2
4 mg/24 hours	9 mg	20 cm^2
6 mg/24 hours	13.5 mg	30 cm^2

System Components and Structure

Neupro is a thin, matrix-type transdermal system composed of three layers:



Backing film

Drug matrix

Protective liner

1. A flexible, tan-colored backing film, consisting of an aluminized polyester film coated with a pigment-layer on the outer side. The backing provides structural support and protection of the drug-loaded adhesive layer from the environment.
2. A self-adhesive drug matrix layer, consisting of the active component rotigotine and the following inactive components: ascorbyl palmitate, povidone, silicone adhesive, sodium metabisulfite, and dl-alpha-tocopherol.
3. A protective liner, consisting of a transparent fluoropolymer-coated polyester film. This liner protects the adhesive layer during storage and is removed just prior to application.

CLINICAL PHARMACOLOGY

Mechanism of Action

Rotigotine is a non-ergoline $D_3/D_2/D_1$ dopamine agonist for the treatment of Parkinson's disease. The precise mechanism of action of rotigotine as a treatment for Parkinson's disease is unknown although it is thought to be related to its ability to stimulate dopamine D2 receptors within the caudate-putamen in the brain. Rotigotine improved motor deficits in animal models of Parkinson's disease (6-OHDA in rat and MPTP model in monkey) including when administered transdermally

Pharmacokinetics

On average, approximately 45% of the rotigotine from the patch is released within 24 hours (0.2 mg/cm^2). Rotigotine is primarily eliminated in the urine as inactive conjugates. After removal of the patch, plasma levels decreased with a terminal half-life of 5 to 7 hours. The pharmacokinetic profile showed a biphasic elimination with an initial half-life of 3 hours.

Absorption

When single doses of 40 cm^2 systems are applied to the trunk, there is an average lag time of approximately 3 hours until drug is detected in plasma, (range 1 to 8 hours). Tmin occurs most commonly between 0 to 7 hours post dose. Tmax typically occurs between 15 to 18 hours post dose but can occur from 4 to 27 hours post dose. However, there is no characteristic peak concentration observed. Rotigotine displays dose-proportionality over a daily dose range of 2 mg/24 hours to 8 mg/24 hours.

On average, approximately 45% of the rotigotine from the patch is released within 24 hours (0.2 mg/cm^2), independent of patch size. Similar absorption per cm^2 was observed in healthy subjects and patients with early stage Parkinson's disease.

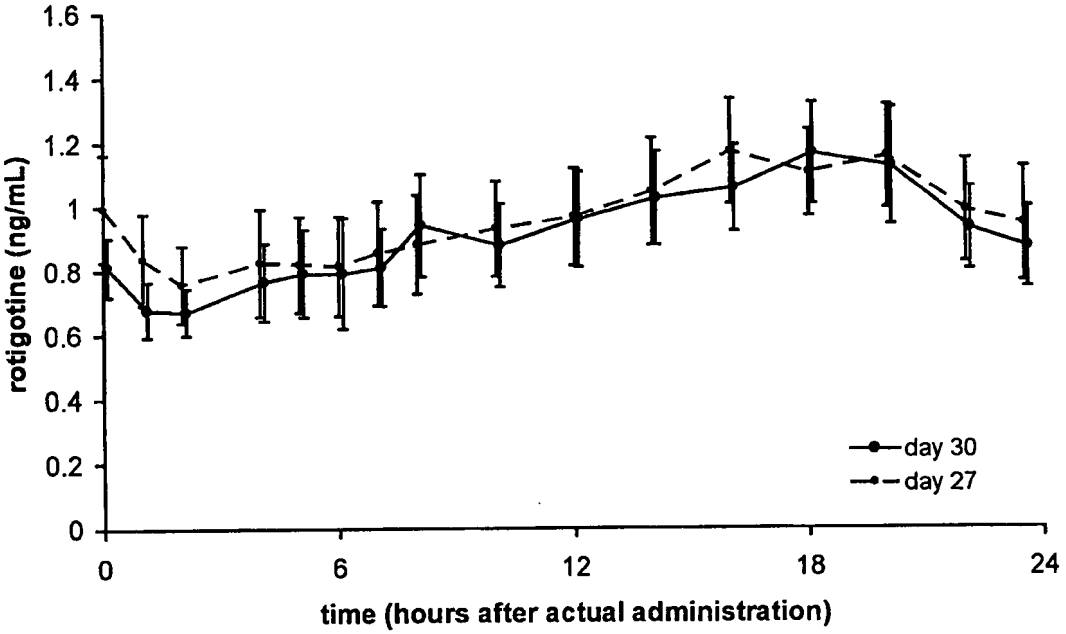
In the clinical studies of rotigotine effectiveness, the transdermal system application site was rotated from day to day (abdomen, thigh, hip, flank, shoulder, or upper arm) and the mean measured plasma concentrations of rotigotine were stable over the six months of maintenance treatment. Relative bioavailability for the different application sites at steady-state was evaluated in subjects with Parkinson's disease. Differences in bioavailability ranged from less

than 1% (abdomen vs hip) to 64% (shoulder vs thigh) with shoulder application showing higher bioavailability.

Because rotigotine is administered transdermally, food should not affect absorption, and the product may be administered without regard to the timing of meals.

In a 14-day clinical study with rotigotine administered to healthy subjects, steady-state plasma concentrations were achieved within 2 to 3 days of daily dosing.

Figure 1 Average (±95% CI) Neupro Plasma Concentrations in Patients with Early-Stage Parkinson's Disease After Application of 8 mg/24 hours to 1 of 6 Application Sites (shoulder, upper arm, flank, hip, abdomen, or thigh) on 2 Different Days During the Maintenance Phase



Distribution

The weight normalized apparent volume of distribution, (Vd/F), in humans is approximately 84 L/kg after repeated dose administration.

The binding of rotigotine to human plasma proteins is approximately 92% *in vitro* and 89.5% *in vivo*.

Metabolism and Elimination

Rotigotine is extensively metabolized by conjugation and N-dealkylation. After intravenous dosing the predominant metabolites in human plasma are sulfate conjugates of rotigotine, glucuronide conjugates of rotigotine, sulfate conjugates of the N-despropyl-rotigotine and

conjugates of N-desthienyl -rotigotine. Multiple CYP isoenzymes, sulfotransferases and two UDP-glucuronosyltransferases catalyze the metabolism of rotigotine (See Drug Interactions)

After removal of the patch, plasma levels decreased with a terminal half-life of 5 to 7 hours. The pharmacokinetic profile showed a biphasic elimination with an initial half-life of 3 hours.

Rotigotine is primarily excreted in urine (~71%) as inactive conjugates of the parent compound and N-desalkyl metabolites. A smaller proportion is excreted in feces (~11%). The major metabolites found in urine were rotigotine sulfate (16% to 22%of the absorbed dose), rotigotine glucuronide (11%-15%), and N-despropyl-rotigotine sulfate metabolite (14% to 20%) and N-desthienylethyl-rotigotine sulfate metabolite (10% to 21%). Approximately 11% is renally eliminated as other metabolites. A small amount of unconjugated rotigotine is renally eliminated (<1% of the absorbed dose).

Pharmacokinetics in Special Populations

Hepatic Insufficiency

The effect of impaired hepatic function on the pharmacokinetics of rotigotine has been studied in subjects with moderate impairment of hepatic function (Child Pugh classification – Grade B). There were no relevant changes in rotigotine plasma concentrations. No dose adjustment is necessary in subjects with moderate impairment of hepatic function. No information is available on subjects with severe impairment of hepatic function. (See **PRECAUTIONS, Hepatic Insufficiency)**

Renal Insufficiency

The effect of renal function on rotigotine pharmacokinetics has been studied in subjects with mild to severe impairment of renal function including subjects requiring dialysis compared to healthy subjects. There were no relevant changes in rotigotine plasma concentrations. In subjects with severe renal impairment not on dialysis, (i.e., creatinine clearance 15 to <30 ml/min), exposure to rotigotine conjugates was doubled. No dosage adjustment is recommended.

Gender

Female and male subjects and patients had similar plasma concentrations (body weight normalized).

Geriatric Patients

Plasma concentrations of rotigotine in patients 65 to 80 years of age were similar to those in younger patients, approximately 40 to 64 years of age. Although not studied, exposures in older subjects (> 80 years) may be higher due to skin changes with aging.

Pediatric Patients

The pharmacokinetics of rotigotine in subjects below the age of 18 years has not been established.

Race

The pharmacokinetic profile was similar in Caucasians, Blacks, and Japanese. No dose adjustment is necessary based on ethnicity.

Adhesion

Adhesion was examined in subjects with Parkinson's disease when patches were applied to rotating sites. Similar results were observed for the 4 mg/24 hours (20 cm^2), 6 mg/24 hours (30 cm^2), and 8 mg/24 hours (40 cm^2) patches. An adherence of ≥90% of the patch surface was observed in 71% to 82% of cases. A partial detachment of >10% was observed in 15% to 24% of cases. A complete detachment of the patch was observed in 3% to 5% of cases.

CLINICAL STUDIES

The effectiveness of Neupro in the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease was evaluated in three parallel group, randomized, double-blind placebo controlled studies conducted in the U.S. and abroad. These studies were conducted in patients who were not receiving concomitant dopamine agonist therapy and, who were either L-dopa naïve or off L-dopa for at least 28 days prior to baseline and were never on L-dopa for more than 6 months. Patients were excluded from the study if they had a history of pallidotomy, thalamotomy, deep brain stimulation, or fetal tissue transplant. Patients receiving selegiline, anticholinergic agents, or amantadine must have been on a stable dose for at least 28 days prior to baseline; they were to attempt to maintain that dose for the duration of the study.

The primary outcome assessment was the change from baseline for the combined scores for Part II (activities of daily living component) plus part III (motor component) of the Unified Parkinson's Disease Rating Scale (UPDRS). Part II of the UPDRS contains 13 questions relating to activities of daily living that are scored from 0 (normal) to 4 (maximal severity) for a maximum (worst) score of 52. Part III of the UPDRS contains 27 questions (for 14 items), each scored 0 (normal) to 4 (maximal severity). Part III is designed to assess the severity of the cardinal motor findings in patients with Parkinson's disease (e.g., tremor, rigidity, bradykinesia, postural instability), scored for different body regions, and has a maximum (worst) score of 108.

<u>Dose-Response Study</u>

This study was a randomized, double-blind, dose-response, multicenter, multinational study in which 316 early stage Parkinson's Disease patients were assigned to treatment with either placebo or one of several fixed doses (2 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, or 8 mg/24 hours) of Neupro, given as 1, 2, 3, or 4 2-mg patches for a period up to 11 weeks. The patches were applied to the upper abdomen and the sites of application were rotated on a daily basis. Patients underwent a weekly titration (increasing the number of 2 mg/24 hours patches or placebo patches at weekly intervals) over 4 weeks such that the target doses of Neupro were achieved for all groups by the end of 3 weeks and were administered over the fourth week of the titration phase. Patients then continued on treatment for a 7 week maintenance phase followed by a down titration during the last week. Two back titrations by a single patch (i.e. 2 mg/24 hours decrement of Neupro or placebo) at a time were permitted for intolerable adverse events.

The mean age of patients was approximately 60 years (range 33 to 83 years; approximately 36 % were ≥ 65 years) and the study enrolled more men (62 %) than women (39 %). Most patients (85 %) were Caucasian and most randomized patients (≥ 88 %) completed the full treatment period.

Mean baseline combined UPDRS (Parts II + III) scores were similar among all treatment groups, between 27.1 and 28.5 for all groups. Patients experienced a mean improvement (i.e. reductions) in the combined UPDRS (Parts II + III) from baseline to end of treatment (end of week 11 or last visit for patients discontinuing early) of -3.5, -4.5, -6.3, and -6.3 for the 2 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, and 8 mg/24 hours Neupro groups respectively and –1.4 for the placebo group. The difference from the placebo group for the mean change for each Neupro dose is shown in Table 2. Statistically significant mean changes reflecting dose-related improvement were observed at the three highest doses, and the 6 mg/24 hours and 8 mg/24 hours doses had a similar effect.

Table 2 Dose-Response Study: Mean Change in UPDRS (Parts II + III) from Baseline at End of Treatment for Intent-to-Treat Population

Neupro Nominal Dose	Rotigotine Content per System	Difference from placebo
2 mg/24 hours	4.5 mg	-2.1
4 mg/24 hours	9 mg	-3.1
6 mg/24 hours	13.5 mg	-4.9
8 mg/24 hours	18 mg	-5.0

North American Study

This study was a randomized, double-blind, multinational, flexible Neupro dose (2, 4, or 6 mg/24 hours), parallel group study in which 277 early stage, idiopathic Parkinson's Disease patients were assigned (2: 1 ratio) to treatment with Neupro or placebo for a period up to about 28 weeks. This study was conducted in 47 sites in North America (U.S. and Canada). Patches were applied to different body parts including upper or lower abdomen, thigh, hip, flank, shoulder, and/ or upper arm and patch application sites were to be rotated on a daily basis. Patients underwent a weekly titration (consisting of 2 mg/24 hours increments at weekly intervals) over 3 weeks to a maximal dose of 6 mg/24 hours depending on efficacy and tolerability, and then received treatment over a 24 week maintenance phase followed by a de-escalation over a period up to 4 days. Back/down titration by a single patch (i.e. 2 mg/24 hours decrement of Neupro or placebo) was permitted during the titration phase for intolerable adverse events but was not permitted during the maintenance phase (i.e., patients with intolerable adverse events had to leave the study). Primary efficacy data were collected after a treatment period of up to approximately 27 weeks.

The mean age of patients was approximately 63 years (range 32 to 86 years; approximately 45 % were $\geq$ 65 years), approximately two-thirds of all patients were men, and nearly all patients were Caucasian. Approximately 90 % of patients randomized to Neupro achieved a maximal daily dose of 6 mg/24 hours; 70 % maintained this dose for most (> 20 weeks) of the maintenance phase. Most enrolled patients ($\geq$ 81 %) completed the full treatment period.

Mean baseline combined UPDRS (Parts II + III) was similar in both groups (29.9 Neupro group, 30.0 placebo). Neupro treated patients experienced a mean change in the combined UPDRS (Parts II + III) from baseline to end of treatment (end of treatment week 27 or last visit for patients discontinuing early) of -4.0, and placebo treated patients showed a mean change from baseline of +1.39 , a difference (see Table 3)that was statistically significant.

Table 3 North American Study: Mean Change in UPDRS (Parts II + III) from Baseline at End of Treatment for Intent-to-Treat Population

Neupro Nominal Dose	Rotigotine Content per System	Difference from placebo
Up to 6 mg/24 hours	Up to 13.5 mg	-5.3

Foreign Multinational Study

This study was a randomized, double-blind, multinational, flexible Neupro dose (2 mg/24 hours, 4 mg/2 hours, 6 mg/24 hours, or 8 mg/24 hours), three arm, parallel group, study using a double-dummy treatment in which 561 early stage, Parkinson's Disease patients were assigned to treatment with either placebo or Neupro or active oral comparator in a ratio of 1: 2: 2 for a period up to about 39 weeks. This study was conducted in up to 81 sites in many countries outside of North America. Patches were applied to different body parts including upper or lower abdomen, thigh, hip, flank, shoulder, and/ or upper arm and patch application sites were to be rotated on a daily basis. Treatment with a patch and placebo was given to all patients in a double-blinded manner such that no one would know the actual treatment (i.e. Neupro, comparator, or placebo). Patients underwent a weekly dose escalation of patch (consisting of 2 mg/24 hours increments of Neupro or placebo) and a dose escalation of capsules of comparator or placebo over 13 weeks up to a maximal dose of 8 mg/24 hours of Neupro depending on achieving optimal efficacy or intolerability at a lower dose. Patients randomized to Neupro achieved the maximal dose of 8 mg/24 hours after a 4 week titration if maximal efficacy and intolerability had not occurred over a 4 week titration period. Patients then received treatment over a 24 week maintenance phase followed by a de-escalation over a period up to 12 days. A single back titration by a single patch (i.e. 2 mg/24 hours decrement of Neupro or placebo) or capsule was permitted during the titration phase for intolerable adverse events but was not permitted during the maintenance phase (i.e. patients with intolerable adverse events had to discontinue from this study). Primary efficacy data were collected after a treatment period of up to approximately 37 weeks of randomized treatment.

The mean age of patients was approximately 61 years (range 30 -86 years; approximately 41 % were $\geq$ 65 years), nearly 60 % of all patients were men, and nearly all patients were Caucasian. About 73 % of patients completed the full treatment period. The mean daily dose of Neupro was just less than 8 mg/24 hours and approximately 90 % of patients achieved the maximal daily dose of 8 mg/24 hours.

Mean baseline combined UPDRS (Parts II + III) was similar across all groups (33.2 Neupro, 31.3 placebo, 32.2 comparator). Neupro treated patients experienced a mean change in the combined UPDRS (Parts II + III) from baseline to end of treatment (end of treatment week 37 or last visit for patients discontinuing early) of - 6.83, and placebo treated patients showed a mean change from baseline of – 2.33 (see Table 4), a difference that was statistically significant.

Table 4 Foreign Multinational Study: Mean Change in UPDRS (Parts II + III) from Baseline at End of Treatment for Intent-to-Treat Population

Neupro Nominal Dose	Rotigotine Content per System	Difference from placebo
Up to 8 mg/24 hours	Up to 18 mg	-4.5

INDICATIONS AND USAGE

Neupro is indicated for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease.

The effectiveness of Neupro was demonstrated in randomized, controlled studies in patients with early-stage Parkinson's disease who were not receiving concomitant L-dopa therapy. (See **CLINICAL STUDIES)**

CONTRAINDICATIONS

Neupro is contraindicated in patients who have demonstrated hypersensitivity to rotigotine or the components of the transdermal system.

WARNINGS

Sulfite Sensitivity

Neupro contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Falling Asleep During Activities of Daily Living

Patients treated with Neupro have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Although many of these patients reported somnolence while on Neupro, some perceived no warning signs, such as excessive drowsiness, and believed that they were alert

immediately prior to the event. Some of these events have been reported as late as one year after initiation of treatment.

Somnolence is a common occurrence in patients receiving Neupro. Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of pre-existing somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities. Patients should be advised to exercise caution while driving, operating machines, or working at heights during treatment with Neupro. Patients who have already experienced somnolence and/or an episode of sudden sleep onset should not participate in these activities during treatment with Neupro.

Before initiating treatment with Neupro, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with Neupro such as concomitant sedating medications and the presence of sleep disorders. If a patient develops meaningful daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), Neupro should ordinarily be discontinued (see DOSAGE AND ADMINISTRATION for guidance on discontinuing Neupro). If a decision is made to continue Neupro, patients should be advised not to drive and to avoid other potentially dangerous activities. There is insufficient information to establish whether dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Hallucinations

In three double-blind, placebo-controlled studies in patients with early-stage Parkinson's disease who were not treated with L-dopa, 2.0% (13 of 649) of patients treated with Neupro reported hallucinations compared to 0.7% (2 of 289) of patients on placebo. Hallucinations were of sufficient severity to cause discontinuation of treatment in 0.2% (1 of 649) Neupro treated patients compared to 0% (0 of 289) on placebo.

PRECAUTIONS

General

Symptomatic Hypotension

Dopamine agonists, in clinical studies and clinical experience, appear to impair the systemic regulation of blood pressure, resulting in postural hypotension, especially during dose escalation. Parkinson's disease patients, in addition, appear to have an impaired capacity to respond to a postural challenge. For these reasons, Parkinson's patients being treated with dopaminergic agonists ordinarily (1) require careful monitoring for signs and symptoms of postural hypotension, especially during dose escalation, and (2) should be informed of this risk. (See **PRECAUTIONS, Information for Patients**)

The pooled analyses of a variety of adverse event terms suggestive of orthostatic hypotension in the three controlled efficacy studies showed the incidence of these events with Neupro 6 mg/24 hours was 5%vs 4% for placebo. Examination of systolic blood pressure -decreases of $\geq$20 mmHg at 3 minutes after arising showed an incidence of 5% for Neupro 6 mg/24 hours vs 4%

for placebo. In a separate analysis, decreases in systolic blood pressure from baseline at anytime of $\geq$40 mmHg in the supine position were seen in 7% of subjects who received Neupro 6 mg/24 hours and 4% for placebo.

An analysis of the dose response study using a variety of adverse event terms suggestive of orthostatic hypotension, including dizziness and postural dizziness, showed a 2 fold higher incidence of these events with Neupro (22 %) vs placebo (11 %). This increased risk was observed in a setting in which patients were very carefully titrated, and patients with clinically relevant cardiovascular disease or symptomatic orthostatic hypotension at baseline had been excluded from this study. The study showed a dose-related increased risk for mild-moderate systolic orthostatic hypotension (decrease of $\geq$ 20 mm Hg) at the end of the titration period (after 4 weeks treatment) with the highest recommended 6 mg/24 hours Neupro dose (6 %) vs placebo (3 %) or lower Neupro doses (2 mg/24 hours or 4 mg/24 hours 0 %). An increased dose-related risk (3 % for 4 and 6 mg/24 hours Neupro; 2 % for placebo and 2 mg/24 hours Neupro) of systolic orthostatic hypotension was also observed after 7 weeks of treatment.

Syncope

Syncope has been reported in patients using dopamine agonists, and for this reason patients should be alerted to the possibility of syncope. The reported incidence of syncope was no greater among those receiving Neupro (1%) than among those receiving placebo (1%). Because the studies of Neupro excluded patients with clinically relevant cardiovascular disease, it is not known to what extent the estimated incidence figures apply to Parkinson's disease patients as a whole. Therefore, patients with severe cardiovascular disease should be treated with caution.

Elevation of Heart Rate and Blood Pressure

Neupro on average increased heart rate by 2 to 4 bpm in rotigotine treated patients compared to placebo patients. Subjects who received Neupro in clinical studies had a slightly higher incidence of a heart rate exceeding 100 beats per minute (9% vs 7% of placebo subjects).

Neupro treatment was not associated with a consistent mean change in systolic and diastolic blood pressure. Subjects on Neupro had a higher incidence of systolic blood pressures >180 mm Hg and diastolic blood pressures >105 mmHg compared to placebo (SBP: 4% vs 2%; DBP: 9% vs 5%). In the Dose-Response study, there was a dose-related increase in systolic blood pressure increases $\geq$ 20 mm Hg at the highest recommended Neupro dose (6 mg/24 hours), 12 % vs 9 % for lower doses or placebo when standing at the final visit and 8 % vs 3 % for lower doses or placebo after changing from supine to standing at the final visit. These findings of blood pressure elevations should be considered when treating patients with cardiovascular disease.

Weight Gain and Fluid Retention

Subjects taking Neupro had a higher incidence (3%) of substantial weight gain (more than 10% of baseline weight) than placebo subjects (<1%). This weight gain was frequently associated with the development of peripheral edema, suggesting that Neupro may cause substantial fluid retention in some patients. Although the weight gain was usually well-tolerated in subjects observed in clinical studies, it could cause greater difficulty in patients who may be especially vulnerable to negative clinical consequences from fluid retention such as those with significant congestive heart failure or renal insufficiency.

Dyskinesia

Neupro may potentiate the dopaminergic side effects of L-dopa and may cause and/or exacerbate pre-existing dyskinesia. Dyskinesia was reported at a similar rate in patients treated with Neupro (0.5%) or placebo (0.3%).

Hepatic Insufficiency

No adjustment of the dose is needed in patients with moderate hepatic impairment (Child Pugh classification – Grade B). The pharmacokinetics of rotigotine have not been studied in patients with severe hepatic impairment.

Application Site Reactions

Application site reactions (ASRs) were reported at a greater frequency in the Neupro treated patients (37%, 239/649) than in placebo patients (14%, 40/289) in the three double-blind, placebo-controlled studies with Neupro.

In the Dose-Response study, ASRs exhibited a dose-response relationship for the highest recommended Neupro dose (6 mg/24 hours) not only during the whole study period (placebo 19 %, 2 mg/24 hours 24 %, 4 mg/24 hours 21 %, 6 mg/24 hours 34 %) but also in separate analyses of the titration period and of the maintenance period. ASRs as a cause for study discontinuation also showed a dose-response increased risk for the whole study period for 6 mg/24 hours Neupro vs other treatments (placebo 0%, 2 mg/24 hours 2 %, 4 mg/24 hours 0 %, 6 mg/24 hours 3 %).

Of ASRs in Neupro treated patients, most were mild or moderate in intensity. The signs and symptoms of these reactions generally were localized erythema, edema, or pruritus limited to the patch area and usually did not lead to dose reduction. About 5% of patients treated with Neupro in these studies discontinued as a result of an ASR. Generalized skin reactions (e.g., allergic rash, including erythematous, macular-papular rash, or pruritus), have been reported at lower rates than ASRs during the development of Neupro.

In a clinical study to investigate the cumulative human skin irritation of Neupro, daily rotation of Neupro application sites has been shown to reduce the incidence of ASRs in comparison to repetitive application to the same site. In a clinical study investigating the skin sensitizing potential of Neupro in 221 healthy subjects, no case of contact sensitization was observed. Localized sensitization reactions were observed in a study in normal volunteers with continuous rotating transdermal system application to a 2.5 cm^2 system, (0.5 mg/24 hours), after induction of maximal irritational stress by repetitive transdermal system application to the same site. If a patient reports a persistent application site reaction (of more than a few days), reports an increase in severity, or reports a skin reaction spreading outside the application site, an assessment of the risks and benefits for the individual patient should be conducted. If a generalized skin reaction associated with the use of Neupro is observed, Neupro should be discontinued.

Melanoma

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear.

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using (Neupro) for *any* indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Magnetic Resonance Imaging and Cardioversion

The backing layer of Neupro contains aluminum. To avoid skin burns, Neupro should be removed prior to magnetic resonance imaging or cardioversion.

Heat Application

The effect of application of heat to the transdermal system has not been studied. However, heat application has been shown to increase absorption several fold with other transdermal products. Patients should be advised to avoid exposing the applied Neupro transdermal system to external sources of direct heat, such as heating pads, or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.

Events Reported with Dopaminergic Therapy

Withdrawal-Emergent-Hyperpyrexia and Confusion

Although not reported with Neupro, a symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, rhabdomyolysis, and/or autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in anti-Parkinsonian therapy. Therefore it is recommended that the dose be tapered at the end of Neupro treatment as a prophylactic measure (See **DOSAGE AND ADMINISTRATION** for guidance on discontinuing Neupro).

Fibrotic complications

Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, pleural thickening, pericarditis and cardiac valvulopathy have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur.

Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, nonergot derived dopamine agonists can cause them is unknown.

Binding to Melanin

As has been reported with other dopamine agonists, binding to melanin-containing tissues (i.e., eyes) in the pigmented rat and monkey was evident after a single dose of rotigotine, but was slowly cleared over the 14-day observation period.

Information for Patients

Patients should be instructed to use Neupro only as prescribed.

Patients should be asked about sensitivity to sulfites. Advise patient that Neupro contains sodium metabisulfite, which may cause allergic-type reactions including anaphylactic symptoms and life threatening or less severe asthmatic episodes in certain susceptible people.

Patients should be alerted to the potential sedating effects associated with Neupro, including somnolence and particularly to the possibility of falling asleep while engaged in activities of daily living. Since somnolence is a frequent adverse event with potentially serious consequences, patients should neither drive a car nor engage in other potentially dangerous activities until they

have gained sufficient experience with Neupro to gauge whether or not it affects their mental and/or motor performance adversely. Patients should be advised that if increased somnolence or new episodes of falling asleep during activities of daily living (e.g., watching television, passenger in a car, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician. If patients have previously experienced somnolence and/or have fallen asleep without warning prior to use of Neupro, they should be advised not to drive, operate machinery, or work at heights during treatment.

As Neupro is administered transdermally, food intake and delayed gastric emptying will not influence the rate of absorption.

Patients should be instructed to wear Neupro continuously for 24 hours. After 24 hours, the patch should be removed and a new one applied immediately. Patients can choose the most convenient time of day or night to apply Neupro but should be advised to apply the patch at approximately the same time each day. If a patient forgets to change a patch, a new patch should be applied as soon as possible and replaced at the usual time the following day.

Neupro should be applied once daily to clean, dry, and intact skin on the abdomen, thigh, hip, flank, shoulder, or upper arm. If applied to a hairy area, the area should be shaved at least 3 days prior to applying the patch. Neupro should not be applied to areas that could be rubbed by tight clothing or under a waistband. Neupro should not be applied to skin folds. Neupro should not be applied to skin that is red, irritated, or impaired. Creams, lotions, ointments, oils, and powders should not be applied to the skin area where Neupro will be placed.

Care should be used to avoid dislodging the patch while showering, bathing or during physical activity. After applying Neupro, patients or caregivers should wash their hands to remove any drug and should be careful not to touch their eyes or any objects. If the edges of the patch lift, Neupro may be taped down with bandage tape. If the patch detaches, a new one may be applied immediately to a different site. The patient should then change the patch according to their regular schedule.

Patients should be informed that application site reactions can occur and that the Neupro transdermal system application site should be rotated on a daily basis (e.g., from the right side to the left side and from the upper body to the lower body). Neupro should not be applied to the same application site more than once every 14 days. If a patient reports a persistent application site reaction (of more than a few days), reports an increase in severity, or reports a skin reaction that spreads outside the application site, an assessment of the risk/benefit balance for the individual patient should be conducted. If a generalized skin reaction associated with the use of Neupro is observed, Neupro should be discontinued.

If there is a skin rash or irritation from the transdermal system, direct sunlight on the area should be avoided until the skin heals. Exposure could lead to changes in the skin color.

Neupro should always be removed slowly and carefully to avoid irritation. After removal the patch should be folded over so that it sticks to itself and should be discarded. After removal the application site should be washed with soap and water to remove any drug or adhesive. Baby or mineral oil may be used to remove any excess residue. Alcohol and other solvents (such as nail polish remover) may cause skin irritation and should not be used. Neupro patients or caregivers should wash their hands to remove any drug and should be careful not to touch their eyes or any objects.

Use of Neupro is associated with nausea, vomiting, and general gastrointestinal distress. Nausea and vomiting may occur more frequently during initial therapy and may require dose adjustment.

Patients should be informed that hallucinations can occur during treatment with Neupro.

Although not reported with Neupro at a greater frequency than with placebo, patients using dopamine agonists may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, syncope, and sweating. Parkinson's disease patients, in addition, appear to have an impaired capacity to respond to a postural challenge and orthostatic hypotension may occur more frequently during initial therapy or with an increase in dose at any time.

Because of the possible additive effects, caution should also be used when patients are taking alcohol, sedating medications, or other CNS depressants (e.g., benzodiazepines, antipsychotics, antidepressants, etc.) in combination with Neupro.

Because applying external heat (e.g., a heating pad, sauna, or hot bath) to the transdermal system may increase the amount of drug absorbed, patients should be instructed not to apply heating pads or other sources of heat to the area of the transdermal system. Direct sun exposure of the transdermal system should be avoided.

Patients should be instructed not to cut or damage Neupro.

To avoid potential burns, Neupro patients should be instructed to remove Neupro before undergoing magnetic resonance imaging (MRI) or cardioversion.

Because of the possibility rotigotine might be excreted in human breast milk, patients should be advised to notify their physicians if they intend to breast-feed or are breast-feeding an infant.

Because experience in humans is limited, patients should be advised to notify their physician if they become or plan to become pregnant during therapy. (See **PRECAUTIONS, Pregnancy**)

There have been reports of patients experiencing intense urges to gamble, increased sexual urges, and other intense urges while taking one or more of the medications generally used for the treatment of Parkinson's disease, including Neupro. Although it is not proven that the medications caused these events, these urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped. Prescribers should ask patients about the development of new or increased gambling urges, sexual urges or other urges while being treated with Neupro. Patients should inform their physician if they experience new or increased gambling urges, increased sexual urges or other intense urges while taking Neupro. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking Neupro.

Drug Interactions

CYP Interactions

In vitro studies indicate that multiple CYP-isoforms are capable of catalyzing the metabolism of rotigotine. In human liver microsomes, no extensive inhibition of the metabolism of rotigotine was observed when co-incubated with CYP isoform specific inhibitors. If an individual CYP isoform is inhibited, other isoforms can catalyze rotigotine metabolism.

Rotigotine, the 5-O-glucuronide and its desalkyl and monohydroxy metabolites were analyzed for interactions with the human CYP isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 *in vitro*. Based on these results, no risk for inhibition of CYP1A2, CYP2C9 and

CYP3A4 catalyzed metabolism of other drugs is predicted at therapeutic rotigotine concentrations. There is a low risk of inhibition of CYP2C19 and CYP2D6 catalyzed metabolism of other drugs at therapeutic concentrations.

In human hepatocytes in vitro, there was no indication for induction of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4.

Rotigotine is metabolized by multiple sulfotransferases and two UDP-glucuronosyltransferases (UGT1A9 and UGT2B15). These multiple pathways make it unlikely that inhibition of any one pathway would alter rotigotine concentrations significantly.

Protein Displacement, Warfarin

In vitro, no potential for displacement of warfarin by rotigotine (and vice versa) from their respective human serum albumin binding sites was detected.

Digoxin

The effect of rotigotine t on the pharmacokinetics of digoxin has been investigated *in vitro* in Caco-2 cells. Rotigotine did not influence the P-glycoprotein-mediated transport of digoxin. Therefore, rotigotine would not be expected to affect the pharmacokinetics of digoxin.

Cimetidine

Co-administration of rotigotine (up to 4 mg/24 hours) with cimetidine (400 mg b.i.d.), an inhibitor of CYP1A2, CYP2C19, CYP2D6, and CYP3A4, did not alter the steady-state pharmacokinetics of rotigotine in healthy subjects.

L-dopa

Co-administration of L-dopa/carbidopa (100/25mg b.i.d.) with rotigotine (4 mg/24 hours) had no effect on the steady-state pharmacokinetics of rotigotine; rotigotine had no effect on the pharmacokinetics of L-dopa/carbidopa.

Dopamine Antagonists

It is possible that dopamine antagonists, such as antipsychotics or metoclopramide, could diminish the effectiveness of rotigotine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year subcutaneous carcinogenicity studies of rotigotine were conducted in CD-1 mice at doses of 0, 3, 10 and 30 mg/kg and in Sprague-Dawley rats at doses of 0, 0.3, 1, and 3 mg/kg; in both studies rotigotine was administered once every 48 hours. No significant increases in tumors occurred in the mouse study at doses up to 12 times the maximum recommended human dose (MRHD) of 6 mg/24 hours.

In rats, there were significant increases in Leydig cell tumors in males and uterine tumors (adenocarcinomas, squamous cell carcinomas) in females. These findings are of questionable significance because the endocrine mechanisms believed to be involved in the production of Leydig cell and uterine tumors in rats are not considered relevant to humans. Therefore, there were no significant tumor findings considered relevant to humans at plasma exposures (AUC) up to 5 to 9 times the plasma AUC in humans at the MRHD.

Mutagenesis

Rotigotine was not mutagenic in the *in vitro* Ames test or the *in vivo* Unscheduled DNA Synthesis test in hepatocytes from male Fisher rats. In the *in vitro* mouse lymphoma assay, rotigotine was mutagenic and clastogenic in the presence and absence of metabolic activation. Rotigotine was not clastogenic in the in vivo mouse micronucleus test.

Infertility

When administered to female Sprague-Dawley rats prior to and during mating and through gestation day 7, rotigotine disrupted implantation at subcutaneous (s.c.) doses of 1.5 mg/kg/day (2 times the maximum recommended human dose (MRHD) on a mg/m^2 basis) or greater. There was no no-effect dose. In male rats treated from 70 days prior to and through mating, there was no effect on fertility; however, a decrease in epididymal sperm motility was observed at 15 mg/kg. The no-effect dose was 5 mg/kg/day (8 times the MRHD on a mg/m^2 basis). Rotigotine was administered to female CD-1 mice at s.c. doses of 10, 30, and 90 mg/kg/day (8 to 73 times the MRHD on a mg/m^2 basis) from 2 weeks until 4 days before mating and then at a dose of 6 mg/kg/day (all groups) (5 times the MRHD on a mg/m^2 basis) from 3 days before mating until gestation day 7; disrupted implantation was observed at all doses. The effects on implantation are thought to be due to the prolactin-lowering effect of rotigotine. In humans, chorionic gonadotropin, not prolactin, is essential for implantation.

Pregnancy

Pregnancy Category C

In subcutaneous studies in Sprague-Dawley rats and CD-1 mice, rotigotine was shown to have adverse effects on embryo-fetal development. Rotigotine given to pregnant rats during organogenesis (0.5, 1.5 or 5 mg/kg/day on gestation days 6 through 17) resulted in increased fetal death at all doses. The lowest effect dose was 0.8 times the MRHD on a mg/m^2 basis. This effect is thought to be due to the prolactin-lowering effect of rotigotine. Rotigotine given to pregnant mice during organogenesis (10, 30 or 90 mg/kg/day on gestation days 6 through 15) resulted in an increased incidence of skeletal retardation at 30 and 90 mg/kg/day, and an increase in fetal death at 90 mg/kg/day. No effects were observed at 10 mg/kg/day (8 times the MRHD on a mg/m^2 basis). Rotigotine given to pregnant Himalayan rabbits during organogenesis (1, 5, or 15 mg/kg/day (3-49 times the MRHD on a mg/m^2 basis) on gestation days 6 through 20) had no effects on embryo-fetal development; however, the study was not conducted at sufficiently high doses. In a pre- and postnatal development study, Sprague-Dawley rats were administered 0.1, 0.3 or 1 mg/kg/day from gestation day 6 through postnatal day 21. Rotigotine impaired growth and development of offspring during lactation and produced neurobehavioral abnormalities in offspring at 1 mg/kg/day. When offspring were mated, growth and survival of their offspring were adversely affected. No adverse effects were observed at 0.3 mg/kg/day (0.5 times the maximum recommended human dose on a mg/m^2 basis).

There are no adequate and well-controlled studies using Neupro in pregnant women.

Therefore, the use of Neupro cannot be recommended during pregnancy unless the potential benefits of therapy justify the potential risk to the fetus.

Nursing Mothers

Rotigotine decreases prolactin secretion in humans and could potentially inhibit lactation.

Studies in rats have shown that rotigotine and/or its metabolite(s) is excreted in breast milk. It is not known whether rotigotine is excreted in human breast milk. Because of the possibility that rotigotine may be excreted in human milk, and because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use

Safety and effectiveness in pediatric patients have not been established.

Geriatric use

Of the subjects treated with Neupro in clinical studies for treatment of early-stage Parkinson's disease, 42% were 65 years old and over, and 9% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

No overall differences in plasma levels of rotigotine were observed between patients who were 65 to 80 years old compared with younger patients receiving the same rotigotine doses. (See **CLINICAL PHARMACOLOGY, Geriatric Patients)**

ADVERSE REACTIONS

The safety of Neupro was evaluated in a total of 649 patients who participated in three double-blind, placebo-controlled studies with durations of 3 to 9 months in patients with early-stage Parkinson's disease. Additional safety information was collected in earlier short term studies, and two open-label extension studies in patients with early-stage Parkinson's Disease.

In the 3 double-blind, placebo-controlled studies in patients with early-stage Parkinson's disease, the most commonly observed AEs (incidence ≥5%) that appeared substantially more frequently in the rotigotine groups than in the placebo groups were nausea, application site reaction, somnolence, dizziness, headache, vomiting, and insomnia.

Approximately 13% of 649 rotigotine-treated patients who participated in the 3 longest controlled studies discontinued treatment because of AEs, compared with 6% of 289 patients who received placebo. The adverse events most commonly causing discontinuation of treatment were: application site reaction (5% vs 0% on placebo), nausea (2% vs 0% on placebo), and vomiting (1% vs 0% on placebo).

Adverse Events Incidence in Controlled Clinical Studies in Early-Stage Parkinson's Disease

Table 5 lists treatment-emergent adverse events that occurred in the three placebo-controlled studies in early-stage Parkinson's disease in ≥2% of the patients treated with Neupro and were more frequent than in the placebo group. In these studies, patients did not receive concomitant L-dopa.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse reactions in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies

cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and no-drug factors to the adverse-events incidence rate in the population studied.

Table 5 Treatment-Emergent Adverse Event (Regardless of Causal Relationship) Incidence in Double-Blind, Placebo-Controlled Early-Stage Parkinson's Disease Studies (Events ≥2% of Subjects Treated with Neupro and Numerically More Frequent Than in the Placebo Group)

Body system/preferred term	Placebo N=289 (%)	Neupro N=649 (%)
Application site reactions	14	37
Autonomic nervous system		
Sweating increased	2	4
Mouth dry	1	3
Body as a Whole		
Fatigue	7	8
Accident NOS	4	5
Cardiovascular		
Extremity edema	6	7
Hypertension	2	3
Central and peripheral nervous system		
Dizziness	11	18
Headache	10	14
Vertigo	2	3
Gastrointestinal system		
Nausea	15	38
Vomiting	2	13
Constipation	4	5
Dyspepsia	1	4
Anorexia	1	3
Musculoskeletal system		
Back pain	5	6
Arthralgia	3	4
Psychiatric		
Somnolence	16	25
Insomnia	5	10

Body system/preferred term	Placebo N=289 (%)	Neupro N=649 (%)
Dreaming abnormal	<1	3
Hallucination	1	2
Respiratory system - Sinusitis	2	3
Skin and appendage – erythematous rash	1	2
Urinary tract infection	1	3
Vision abnormal	1	3

NOS=not otherwise specified

Other AEs reported by more than 2% of patients with early-stage Parkinson's disease treated with rotigotine (as displayed), but that were equally or more frequent in the placebo group (after rounding) were: asthenia, influenza-like symptoms, diarrhea, depression, rhinitis, micturition frequency, upper respiratory tract infection, fall, tremor, coughing, anxiety, abdominal pain, and chest pain.

The incidence of AEs was not materially different between men and women in the pooled studies presented in Table 5.

Dose-Related Adverse Events

Many AEs appeared to be dose-related . Table 6 illustrates AEs that were dose-related based upon the highest frequency of AEs occurring with the 6 mg/24 hours dose or with the 4 and 6 mg/24 hours doses compared to the frequency for placebo and the 2 mg/24 hours dose. Rates for the non-recommended 8 mg/24 hr. dose are also shown. Some AEs (anorexia; constipation; vision abnormal) were found to be dose-related only when their onset was in the titration period. Dizziness was only dose-related when it had its onset in the maintenance period.

Table 6 Incidence (%) of Neupro Dose-Related Treatment-Emergent Adverse Events During the Whole Study Period in the Dose-Response Study

Preferred Term Adverse Event	Placebo N = 64	Daily Neupro Dose			
		2 mg/24 hours N = 67	4 mg/24 hours N = 63	6 mg/24 hours N = 65	8 mg/24 hours N = 70
Application site reaction	19	24	21	34	46
Nausea	11	34	38	48	41
Vomiting	3	10	16	20	11
Weight decrease	0	0	0	2	3
Myalgia	0	0	2	2	3
Somnolence	3	13	16	19	21
Insomnia	8	6	13	14	14

Dreaming abnormal	0	2	5	3	7
Hallucination	2	0	2	3	3
Rash erythematous	2	2	6	3	3

690

691

692 Laboratory changes

693 Subjects who received Neupro experienced an average decline in blood hemoglobin levels of
694 about 2% or 0.3 g/dL relative to subjects who received placebo. A decline in blood hemoglobin
695 from baseline of 2 g/dL or more was seen in 4% with Neupro and 1% with placebo. Among
696 subjects with normal baseline hemoglobin levels, about 8% of those who received Neupro
697 developed low hemoglobin levels compared to 5% with placebo. Subjects receiving Neupro who
698 experienced declines in blood hemoglobin were also noted to have declines in serum albumin. It
699 is not known whether these changes are readily reversible with discontinuation of Neupro.

700 Subjects who received Neupro also experienced an average increase in blood urea nitrogen
701 (BUN) levels of about 3.7% or 0.21 mg/dL relative to subjects who received placebo. There was
702 also a higher incidence of abnormally elevated levels of BUN associated with treatment. There
703 were no significant differences between Neupro and placebo in levels of serum creatinine. It is
704 not known whether these changes are readily reversible with discontinuation of Neupro or
705 whether they represent changes in renal function.

706 Treatment with Neupro was associated with a greater likelihood of low levels of blood glucose
707 (less than 50 mg/dL). Among subjects with normal baseline glucose levels, about 7% of subjects
708 who received Neupro developed at least one low blood glucose level compared to 4% with
709 placebo.

710 **Other Adverse Reactions Observed in Subjects with Early-Stage Parkinson's**
711 **Disease during Phase 2 and 3 Studies**

712 Rotigotine was administered to 1220 subjects with early-stage Parkinson's disease in Phase 2
713 and 3 clinical studies, including 6 double-blind, placebo-controlled studies; 319 were in an open-
714 label study in patients with early-stage Parkinson's disease. Adverse events occurring in
715 rotigotine treated patients at least twice, or if the AE was serious, at least once, and events not
716 described elsewhere in labeling, are provided in the following listing. Events too poorly
717 described or not plausibly related to treatment were also omitted. Events are further classified
718 within body system categories and enumerated in order of decreasing frequency using the
719 following definitions: frequent AEs are defined as those occurring in at least 1/100 patients;
720 infrequent AEs are those occurring in 1/100 to 1/1000 patients; and rare events are those
721 occurring in fewer than 1/1000 patients.

722 **Application site disorders:** *frequent* –contact dermatitis

723 **Autonomic nervous system:** *infrequent* – saliva increased, appetite increased, impotence,
724 flushing

725 **Body as a whole:** *frequent* –leg pain, malaise, fever; *infrequent* – allergic reaction, rigors, hot
726 flushes, hyperesthesia

727 **Cardiovascular disorders, general:** *frequent* –syncope; *infrequent* –cardiac failure

Central and peripheral nervous system disorders: *frequent* – paresthesia, confusion, ataxia, gait abnormal, neuralgia, hypoesthesia, hypertonia; *rare*-convulsions

Hearing and vestibular disorders: *infrequent* – tinnitus

Heart rate and rhythm disorders: *infrequent* –, AV (atrioventricular) block, bundle branch block, fibrillation atrial; *rare* – arrhythmia ventricular, tachycardia ventricular

Hematologic disorders: *infrequent* – thrombocytopenia

Liver and biliary disorders: *frequent* – GGT (gamma-glutamyl transferase) increased

Metabolic and nutritional disorders: *frequent* – weight increase

Psychiatric disorders: *infrequent* –paranoid reaction, psychosis

Skin and appendage disorders: *frequent* –pruritus

Urinary system disorders: *frequent* – urinary incontinence

Vascular disorders: *frequent* – purpura

Vision disorders: *infrequent* – photopsia

OVERDOSAGE

There were no reports of overdose of Neupro in the clinical studies.

Since Neupro is a transdermal system, overdosing is not likely to occur in clinical practice unless patients forget to remove the previous day's transdermal system; patients should be warned against this possibility.

Overdose Management

There is no known antidote for overdosage of dopamine agonists. In case of suspected overdose, the transdermal system(s) should immediately be removed from the patient. Concentrations of rotigotine decrease after patch removal. The terminal half-life of rotigotine is 5 to 7 hours. If it is necessary to discontinue use of rotigotine after overdose, it should be discontinued gradually to prevent neuroleptic malignant syndrome. (See **PRECAUTIONS**) The daily dose should be reduced by 2 mg/24 hours with a dose reduction preferably every other day, until complete withdrawal of rotigotine is achieved. Before completely stopping use of Neupro in the event of an overdose, please consult the **DOSAGE AND ADMINISTRATION** section.

The predominant symptoms of overdose with Neupro are expected to be nausea, vomiting, hypotension, involuntary movements, hallucinations, confusion, convulsions, and other signs of excessive dopaminergic stimulation.

The patient should be monitored closely, including heart rate, heart rhythm, and blood pressure. As shown in a study of renally impaired patients, dialysis is not expected to be beneficial. Treatment of overdose may require general supportive measures to maintain vital signs.

DOSAGE AND ADMINISTRATION

Initiation of Therapy

Neupro should be started at 2 mg/24 hours. Based upon individual patient clinical response and tolerability, Neupro dosage may be increased weekly by 2 mg/24 hours if tolerated and if additional therapeutic effect is needed. The lowest effective dose was 4 mg/24 hours. The

highest recommended dose is 6 mg/24 hours. Doses above 6 mg/24 hours have not shown any additional therapeutic benefit (See **CLINICAL STUDIES**, Dose-Response Study) and are associated with an increased incidence of adverse reactions (see Adverse Reactions) If it is necessary to discontinue use of Neupro, it should be discontinued gradually. The daily dose should be reduced by 2 mg/24 hours with a dose reduction preferably every other day, until complete withdrawal of Neupro. (see Precautions; Withdrawal-Emergent-Hyperpyrexia and Confusion)

Administration of transdermal system

Neupro is applied once-a-day. The adhesive side of the transdermal system should be applied to clean, dry, intact healthy skin on the front of the abdomen, thigh, hip, flank, shoulder, or upper arm. The transdermal system should be applied at approximately the same time every day, at a convenient time for the patient. Because Neupro is administered transdermally, food is not expected to affect absorption and it can be applied irrespective of the timing of meals. No dosage adjustment is necessary for patients who have moderate impairment of hepatic function or mild to severe impairment of renal function.

The application site for Neupro should be moved on a daily basis (for example, from the right side to the left side and from the upper body to the lower body). Neupro should not be applied to the same application site more than once every 14 days and should not be placed on skin that is oily, irritated, or damaged, or where it will be rubbed by tight clothing. If it is necessary to apply Neupro to a hairy area, the area should be shaved at least 3 days prior to Neupro application. The system should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place for 20 to 30 seconds, making sure there is good contact, especially around the edges. If the patient forgets to replace Neupro, or if the transdermal system becomes dislodged, another transdermal system should be applied for the remainder of the day.

Complete instructions to facilitate patient counseling on proper usage may be found in the **PRECAUTIONS, Information for Patients** section and in the **PATIENT INFORMATION LEAFLET.**

Animal Toxicology

Retinal Pathology: Albino rats: Retinal degeneration was observed in albino rats in the 6-month toxicity study at the highest dose tested. Retinal degeneration was not observed in the 2-year carcinogenicity studies in albino rat (at plasma exposures (AUC) up to 5 to 9 times the plasma AUC in humans at the MRHD of 6 mg/24 hours) and albino mouse, or in monkeys treated for 1 year. The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (i.e., disk shedding) may be involved.

HOW SUPPLIED

Neupro® is available in 3 strengths, as described in Table 7:

Table 7 Transdermal System Size, Drug Content, and Nominal Delivery Rate

Neupro Nominal Dose	Rotigotine Content per System	Neupro System Size
2 mg/24 hours	4.5 mg	10 cm^2
4 mg/24 hours	9 mg	20 cm^2
6 mg/24 hours	13.5 mg	30 cm^2

Each transdermal system is packaged in a separate pouch.

Each strength is available in cartons of 7 and 30 transdermal systems.

2 mg/24 hours 7 transdermal systems	NDC # 0091-6486-21
2 mg/24 hours 30 transdermal systems	NDC # 0091-6486-01
4 mg/24 hours 7 transdermal systems	NDC # 0091-6487-21
4 mg/24 hours 30 transdermal systems	NDC # 0091-6487-01
6 mg/24 hours 7 transdermal systems	NDC # 0091-6488-21
6 mg/24 hours 30 transdermal systems	NDC # 0091-6488-01

Storage

Store at 20° - 25°C (68° - 77°F); excursions permitted between 15° - 30°C (59° - 86°F). [See USP Controlled Room Temperature]

Neupro should be stored in the original pouch. Do not store outside of pouch.

Apply the transdermal system immediately upon removal from the pouch.

Manufactured for:
SCHWARZ PHARMA, LLC
Mequon, WI 53092, USA

By:
LTS Lohmann Therapie System AG
Lohmannstrasse 2
D-56626 Andernach, Germany

PC4862
Rev. 07/04

PATIENT INFORMATION
NEUPRO® [NU pro]
(rotigotine transdermal system)

Rx Only

IMPORTANT: NEUPRO is for use on the skin only.

Read the Patient Information that comes with NEUPRO before you start using it and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment. If you have any questions about NEUPRO, ask your doctor or pharmacist.

What is the most important information I should know about NEUPRO?

NEUPRO may make you very sleepy or cause you to fall asleep suddenly, and without warning while doing normal activities such as driving, talking with other people, watching TV, or eating. This can happen any time during treatment with NEUPRO.

- Do not drive, work on ladders, or do other dangerous activities while using NEUPRO until you know how NEUPRO affects you.
- If NEUPRO does make you very sleepy, or you fall asleep suddenly while doing normal activities, do not drive or do other dangerous activities until you talk with your doctor.

Tell your doctor if you fall asleep suddenly while doing normal activities or feel sleepier than normal.

Heat may cause too much medicine from a Neupro patch to pass through your skin. While you are wearing a NEUPRO patch, do not:

- **apply a heating pad to the application site area**
- **take a hot bath**
- **use a sauna**
- **expose the application site to direct sunlight**

What is NEUPRO?

NEUPRO is a type of medicine called a dopamine agonist. NEUPRO is a patch (transdermal delivery system) worn on the skin. It is used to treat the signs and symptoms of early-stage Parkinson's disease in adults.
NEUPRO has not been studied in children.

Who should not use NEUPRO?

Do not use NEUPRO if you are allergic to anything in it. See the end of this leaflet for a complete list of ingredients in NEUPRO.

NEUPRO contains a sulfite called sodium metabisulfate. Sulfites can cause life-threatening allergic reactions in people that are sensitive to sulfites. People with asthma are more likely to be sensitive to sulfites. If you have trouble breathing or swallowing while using NEUPRO, remove NEUPRO right away and call your doctor or get emergency care.

NEUPRO may not be right for you. Before starting NEUPRO tell your doctor about all of your health conditions including if you:

- are allergic to sulfites
- have asthma
- have blood pressure problems
- have heart problems
- are pregnant or breastfeeding or planning on becoming pregnant

Tell your doctor if you drink alcohol
Alcohol should be avoided while using NEUPRO. ALCOHOL and NEUPRO can interact and increase your chance of being sleepy or falling asleep suddenly while doing normal activities.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Some medicines may affect how NEUPRO works. NEUPRO may also affect how your other medicines work. **Especially tell your doctor if you take other medicines that can make you sleepy such as sleep medicines, antidepressants, or antipsychotics.**

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I use NEUPRO?

See the end of this leaflet for complete instructions "How to use and apply a NEUPRO patch."

- Use NEUPRO exactly as prescribed by your doctor.
- NEUPRO comes in 4 different size (dose) patches. Your doctor will probably start you on a low dose of NEUPRO. Your doctor will change the dose weekly until you are taking the right amount of medicine to control your symptoms. It may take several weeks before you reach the dose that controls your symptoms best. Do not stop or change your dose of NEUPRO without first talking with your doctor.
- Talk to your doctor often about your condition. **Do not stop or change your treatment with Neupro without talking to your doctor.**
- **Patients with Parkinson's disease may have an increased chance of getting a skin cancer called melanoma. People with Parkinson's disease should have a doctor check their skin for skin cancer regularly.**

What are the possible side effects of NEUPRO?

Possible serious side effects with NEUPRO include:

- **falling asleep while do normal activities.** See "What is the most important information I should know about NEUPRO?"
- **low blood pressure** that makes you feel dizzy, faint, sweaty, or have nausea. Stand up slowly when getting up from a sitting or lying position. Tell you doctor if you if you have symptoms of low blood pressure with NEUPRO.
- **fainting**
- **hallucinations** (seeing, hearing, or sensing things that are not real). The chance for hallucinations is higher in elderly patients with Parkinson's disease.
- **compulsive** behavior and trouble controlling strong urges such as:
  - gambling too much
  - increased sexual desire
  - repeating meaningless actions

Talk to your doctor if you or family members notice that you are having unusual urges

-

The most common side effects with NEUPRO are:

- nausea
- application site reaction
- drowsiness or sleepiness
- dizziness
- headache
- vomiting
- trouble sleeping (insomnia)

These are not all the side effects of NEUPRO. For more information, ask your doctor or pharmacist. Talk to your doctor about any side effects or problems you may have.

How do I store NEUPRO?

- Store NEUPRO at 68° to 77°F (20° to 25°C).
- Store NEUPRO in its sealed pouch until use.
- **Keep NEUPRO and all medicines out of reach of children and away from pets.**

General information about NEUPRO

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use NEUPRO for a condition for which it was not prescribed. Do not give NEUPRO to other people even if they have the same condition you have. It may harm them.

This leaflet summarizes important information about NEUPRO. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about NEUPRO that was written for healthcare professionals.

For more information, visit www.website.com or call 1-800-xxx-xxxx.

What are the ingredients in NEUPRO?

Active ingredient: rotigotine

Inactive ingredients: ascorbyl palmitate, povidone, silicone adhesive, sodium metabisulfite, and dl-alpha-tocopherol.

How to use and apply a NEUPRO patch

Read these instructions carefully before you apply NEUPRO. Ask your doctor or pharmacist about anything you do not understand.

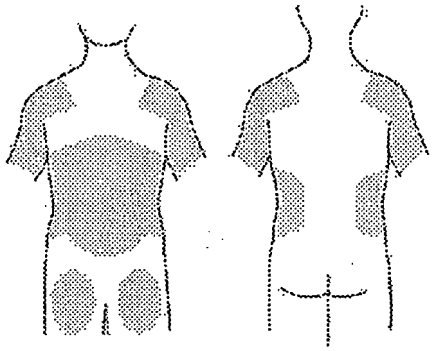
When to Apply NEUPRO:

Each patch is sealed in a pouch that protects it until you are ready to apply it.

- NEUPRO should be applied right away after removing it from the protective pouch.
- Wear NEUPRO for 24 hours. After 24 hours, remove the patch and apply a new one right away to a different area of skin.
- Choose the time of day or night that works best for you to apply NEUPRO. Apply the patch at the same time each day.

Where to Apply NEUPRO:

- Choose an area of clean, dry, and healthy skin on the stomach, thigh, hip, flank (side of the body between the ribs and the pelvis), shoulder, or upper arm.



- If you need to apply the patch to a hairy area, the area should be shaved at least 3 days before applying the patch.
- The patch should not be applied to areas where it could be rubbed by tight clothing or under a waistband.
- Avoid applying the patch on skin folds.
- Do not apply the patch to skin that is red, irritated, or injured.
- Each patch should be applied to a different place on the skin each day, for example, from the right side to the left side and from the upper body to the lower body.

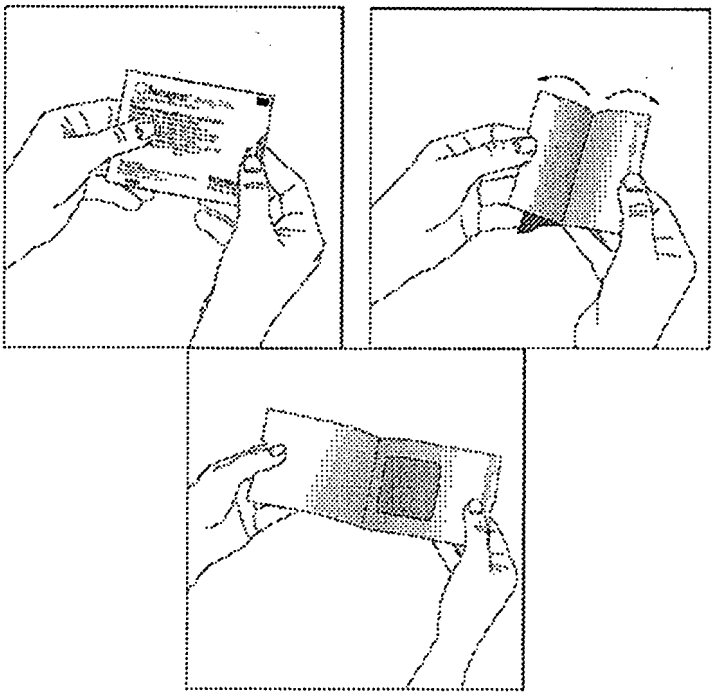
NEUPRO should not be applied to the same area of skin more than once every 14 days.

- Creams, lotions, ointments, oils, and powders should not be applied to the skin area where the patch will be placed.

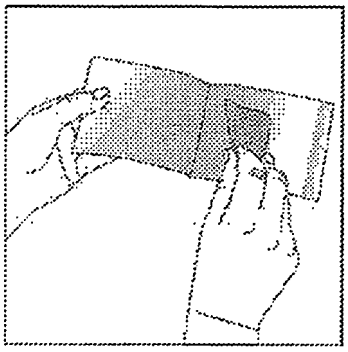
How to Apply NEUPRO:

Each patch is individually packaged. Just before you apply the patch, remove it from its sealed pouch, remove the protective liner and apply to the skin right away. Do not store the patch outside the sealed pouch. Do not cut a NEUPRO patch into smaller pieces.

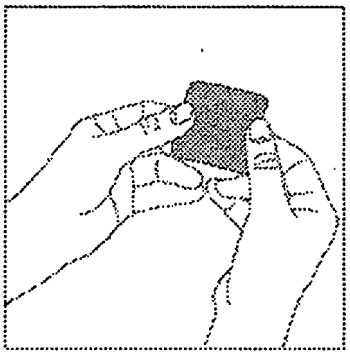
1. Grasp the two sides of the pouch and pull apart.



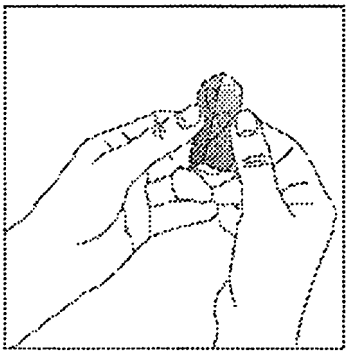
2. Remove the patch from the pouch.



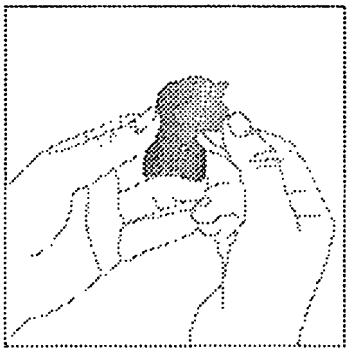
3. Hold the patch with both hands, with the protective liner on top.



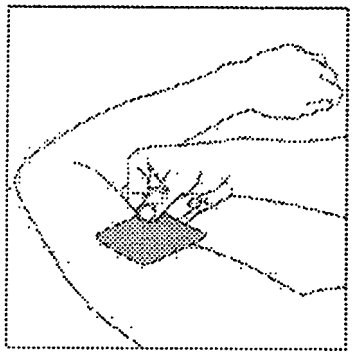
4. Bend the edges of the patch away from you so that the S-shaped cut in the liner opens up.

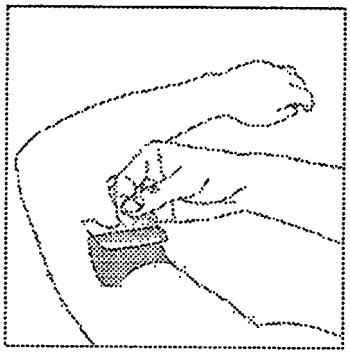


5. Peel off one half of the protective liner. **Do not touch the sticky surface because the medicine could come off on your fingers.**

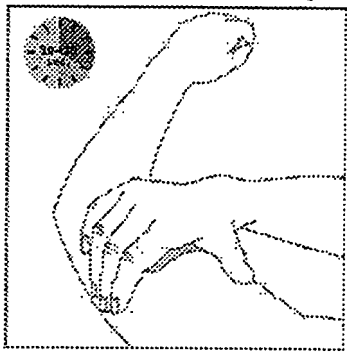


6. Apply the sticky half of the patch to a clean area of skin and remove the remaining liner.





7. Press the patch firmly with the palm of your hand for **20 to 30** seconds to make sure there is good contact with the skin, especially around the edges. Make sure that the patch is flat against the skin (there should be no bumps or fold in the patch).



8. Be sure to wash your hands with soap and water right after handling the patch to remove any medicine that may have gotten on them. Do not touch your eyes until after you have washed your hands.

How to Remove NEUPRO:

1. Slowly and carefully peel off the used patch. Carefully fold it in half (sticky sides together) and throw away the folded patch so that children and pets cannot reach it. This patch still contains some medicine and could harm a child or pet.
2. Gently wash the area with warm water and mild soap to remove any sticky material (adhesive) that stays on your skin. Baby or mineral oil may also be used to remove any adhesive. Alcohol or other solvents, such as nail polish remover, may cause skin irritation and should not be used.
3. Wash your hands with soap and water.
4. You may see mild redness at the site when a patch is removed. This redness should go away over time. If irritation or itchiness continues, tell your doctor.

Other Information:

- Heat may cause too much medicine from a Neupro patch to pass through your skin. While you are wearing a NEUPRO patch, do not:
  - apply a heating pad to the application site area
  - take a hot bath

  - use a sauna
  - expose the application site to direct sunlight
- You may bathe, shower, or swim while wearing a NEUPRO patch. Water may loosen your NEUPRO patch. If a NEUPRO patch falls off, apply a new NEUPRO patch for the rest of the day. The following day, apply a new patch at your regular time.
- If you forget to apply a NEUPRO patch at the usual time, remove the used NEUPRO patch you are currently wearing and put on a new NEUPRO patch on a different area of skin. Then apply a new NEUPRO patch the next day at your regular time.
- If you develop a skin rash or irritation from the patch, avoid direct sunlight on the area until the skin heals because sun exposure could lead to changes of skin color.
- Do not cut or damage a NEUPRO patch.
- To avoid a possible burn on your skin, remove your NEUPRO patch before you have procedures called magnetic resonance imaging (MRI) or a cardioversion.

Distributed by:

SCHWARZ PHARMA, LLC
Mequon, WI 53092

PC4803
Rev. 06/06

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Temple
5/9/2007 04:30:49 PM

EXHIBIT G

US006884434B1

(12) **United States Patent**
Muller et al.

(10) **Patent No.: US 6,884,434 B1**
(45) **Date of Patent: Apr. 26, 2005**

(54) **TRANSDERMAL THERAPEUTIC SYSTEM WHICH CONTAINS A D2 AGONIST AND WHICH IS PROVIDED FOR TREATING PARKINSONISM, AND A METHOD FOR THE PRODUCTION THEREOF**

(75) Inventors: **Walter Muller**, Neuwied (DE); **James V. Peck**, Richmond, VA (US)

(73) Assignees: **LTS Lohmann Therapie-Systeme AG**, Andernach (DE); **Aderis Pharmaceuticals, Inc.**, Richmond, VA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/647,290**

(22) PCT Filed: **Mar. 18, 1999**

(86) PCT No.: **PCT/EP99/01795**

§ 371 (c)(1),
(2), (4) Date: **Nov. 28, 2000**

(87) PCT Pub. No.: **WO99/49852**

PCT Pub. Date: **Oct. 7, 1999**

(30) **Foreign Application Priority Data**

Mar. 30, 1998 (DE) 198 14 084

(51) **Int. Cl.**[7] **A61K 9/14**; A61F 13/00; A61F 13/02; A61L 15/16

(52) **U.S. Cl.** **424/487**; 424/486; 424/485; 424/484; 424/448; 424/449

(58) **Field of Search** 424/487, 486, 424/485, 484, 448, 449, 443; 514/460, 946

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,043,482 A * 8/1991 Maignan et al. 568/734
5,382,596 A * 1/1995 Sleevi et al. 514/459

FOREIGN PATENT DOCUMENTS

EP	WO 94/07468	* 4/1994
WO	0180377	9/1991
WO	WO9407468	4/1994
WO	0524776 B1	8/1995
WO	96/39136	12/1996
WO	97/11696	4/1997

OTHER PUBLICATIONS

Chiang C.M. et al. "A two-phase matrix for the delivery of N-0923, a dopamine agonist", Proc. Int. Symp. Controlled Release Bioact. Mater. 1995 22 nd 710-711.*

Izaak den Daas et al., "Transdermal administeration of the dopamine agonist N-0437 and seven ester prodrugs:comparison with oral administeration in the 6-OHDA turning model", Naunyn-Schmiedegerg's pharmacol (1990) 342: 655-659.*

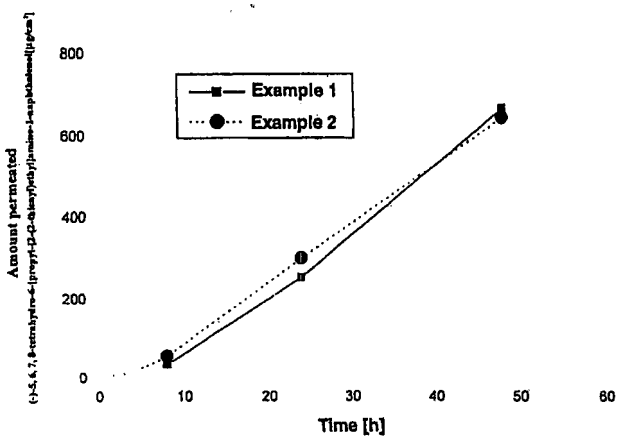
(Continued)

Primary Examiner—Thurman K. Page
Assistant Examiner—Isis Ghali
(74) *Attorney, Agent, or Firm*—Jordan and Hamburg LLP

(57) **ABSTRACT**

A transdermal therapeutic system, comprising a backing layer inert to the components of the matrix, a self-adhesive matrix layer containing (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol in an effective amount and a protective foil or sheet to be removed prior to use, is characterised by a matrix that is based on a non-aqueous, acrylate-based or silicone-based polymer adhesive system having a solubility of ≧5% (w/w) for (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol, and said matrix is substantially free of inorganic silicate particulates.

16 Claims, 1 Drawing Sheet



OTHER PUBLICATIONS

Swart, P. J. et al., "The influence of azone on the transdermal penetration of the dopamine D agonist N–0923 in freely moving rats", Int. J. Pharm. 1992 88 (1–3) 165–170.*

Chiang C.M., et al. "A two–phase matrix for the delivery of N–0923, a dopamine agonist", *Proc. Int. Symp. Controlled Release Bioact. Mater.* 1995 22nd 710–711.

Swart, P.J., et al., "The influence of azone on the transdermal penetration of the dopamine D agonist N–0923 in freely moving rats", *Int. J. Pharm.* 1992 88(1–3) 165–170.

Mar. 14, 1989 Abstract of "Microdialysis and Striatal dopamine release: stereoselective actions of the enantiomers of N–0437" W. Timmerman et al. Eur J. Pharmacol 143–150.

Aug. 18, 1995 Abstract of "Development and validation of a gradient reversed–phase high–performance liquid chromatographic assay for S(–)–2–(N–propyl–N–2–thienylethylamino)–5– hydroxytetralin (n–0923) from a transdermal delivery system" D.L. Walters et al. J. Chromatogr. B. Biomed Appl. 299–307.

Dec. 1990 Abstract of "Transdermal administration of the dopamine agonist N–0437 and seven ester prodrugs: comparison with oral administration in the 6–OHDA turning model" Tepper P.G. den Daas I et al. Naunyn Schmiedebergs Arch Pharmacol 655–659.

Aug. 3, 1989 Abstract of "Stereoselective reversal of MPTP–induced parkinsonism in the marmoset after dermal application of N–0437" P.A. Loschmann et al. Eur J. Pharmacol 373–380.

* cited by examiner

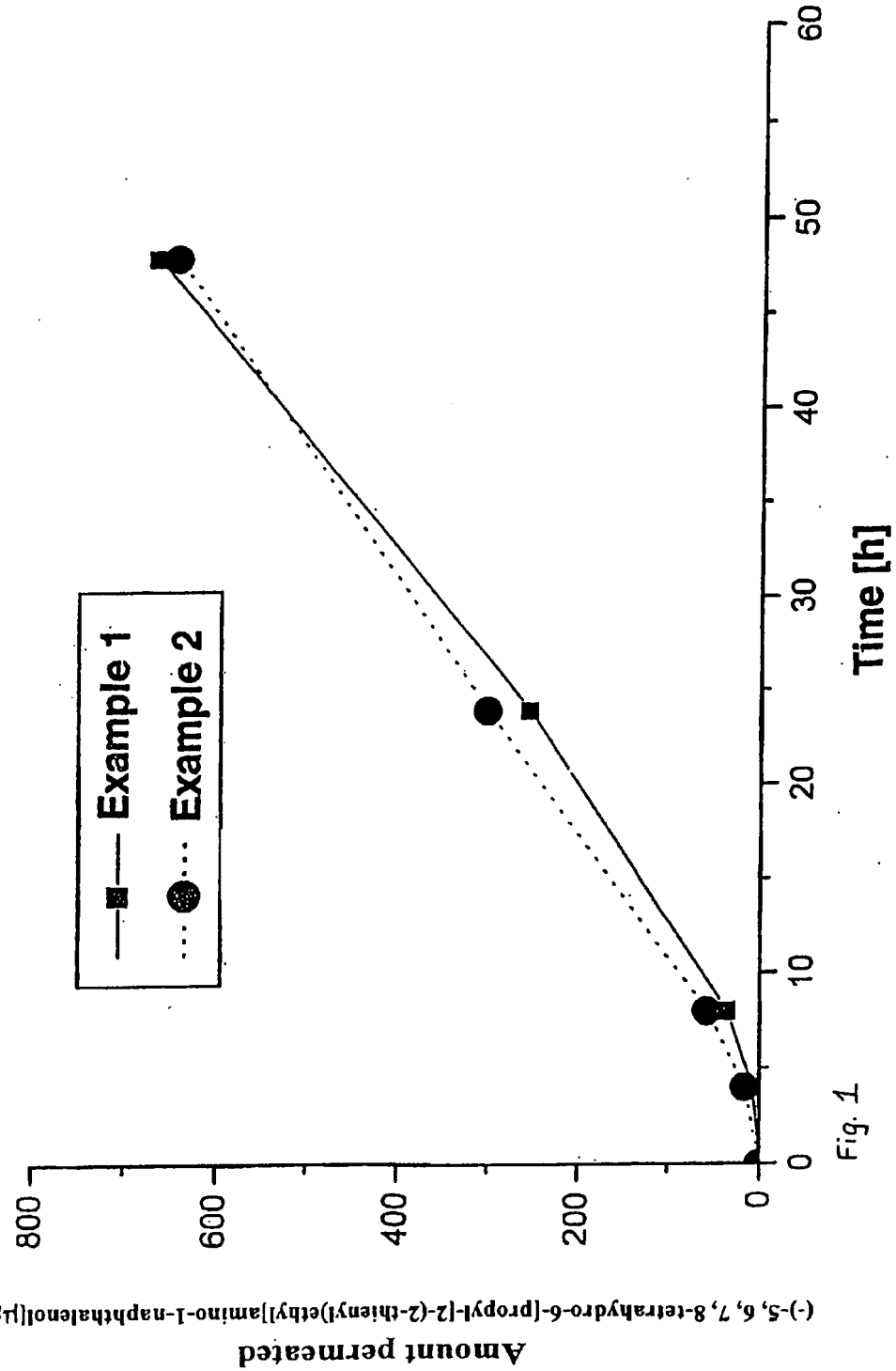
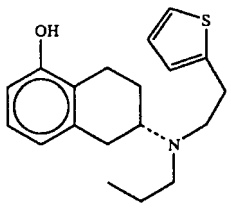

Amount permeated
(-)-5, 6, 7, 8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino-1-naphthalenol[µg/cm²]
800
600
400
200
0
0
10
20
30
40
50
60
Time [h]
Example 1
Example 2

Fig. 1

TRANSDERMAL THERAPEUTIC SYSTEM WHICH CONTAINS A D2 AGONIST AND WHICH IS PROVIDED FOR TREATING PARKINSONISM, AND A METHOD FOR THE PRODUCTION THEREOF

BACKGROUND OF THE INVENTION

The invention relates to a transdermal therapeutic system for the treatment of Parkinson's syndrome, comprising a backing layer which is inert to the ingredients of the matrix, a self-adhesive matrix layer containing (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol having the below-indicated formula



in an effective amount, and a protective layer which is to be removed prior to use.

Worldwide about 2.5–3% of the population suffer from so-called Parkinson's syndrome, which breaks out mainly at the age between 58 and 62. The symptoms of this disease manifest themselves in motorial disorders such as trembling, muscle stiffening, vegetative disorders such as increased flow of saliva and tears, disturbed thermoregulation, hypopiesia and functional disorders of bladder and intestine, as well as psychic disorders such as irresoluteness and depressive mood.

Parkinson's syndrome is caused by the degeneration of dopaminergic neurons in the substantia nigra. This leads to the depletion of dopamine in certain cerebral regions, in particular in the brain stem ganglia. The resultant disturbed balance between the neurotransmitters acetylcholine and dopamine is in the end responsible for the symptoms of the disease. A predominance of acetylcholine is responsible for the so-called plus symptoms, and a deficiency of dopamine is responsible for the so-called minus symptoms.

Parkinson's syndrome can therefore be treated with so-called anticholinergics or levodopa. Anticholinergics impede the cholinergic neurotransmission, and levodopa passes, as precursor of dopamine, the blood-brain barrier and is converted in the brain to dopamine.

Another path of treatment of Parkinson's syndrome is the treatment with dopamine receptor agonists. Dopamine agonists are substances which, although structurally different from dopamine, bind to the same receptors and trigger an effect similar to that of dopamine. Due to their molecular structure dopamine receptor agonists have properties which enable them to overcome the blood-brain barrier. In this connection it is advantageous if the substances bind selectively to a subgroup of the dopamine receptors, the D2-receptors, as this decreases side effects. In this connection, the substance (−)-5,6,7,8 tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol having the above-indicated formula, has proved an especially effective selective D2-agonist.

Due to this compound's half-life and high first-pass effect, oral administration of this substance is, however, very problematic. The short half-life would necessitate frequent intake of the substance, and the high first-pass effect would necessitate high dosage. Whereas the intake frequency may possibly be overcome by an appropriate oral formulation, the problem of high first-pass effect can be solved in principal only by a non-oral administration of the active substance.

A transdermal system designed for the administration of a D2-agonist of the above-indicated formula has already been described in WO 94-07468. This system contains the active substance as hydrochloride in a two-phase matrix which is formed substantially by a hydrophobe polymer material, which is present as a continuous phase, with hydrated silicate dispersed therein for taking up the hydrophile drug salt, and additionally contains, or may contain, hydrophobic solvents, permeation-enhancing agents and dispersing agents.

This system has the disadvantage that the active substance salt must be mixed with the silicate in aqueous solution, and that an additional emulsifier is necessary to emulsify this aqueous solution with the lipophile polymer, which is dissolved in an organic solvent—commonly hexane, heptane or ethyl acetate. Due to coating problems, it is much more difficult to manufacture transdermal systems using this emulsion. In addition, for such systems only the salt can be used, since only the salt is sufficiently hydrophile to be soluble in water.

It is thus the object of the invention to develop systems for (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol avoiding the disadvantages of the system described in WO 94-07468.

In this connection, the invention particularly focuses on optimizing active substance uptake within the system, and skin transfer.

SUMMARY OF THE INVENTION

The transdermal therapeutic system according to this invention, of the kind mentioned at the beginning and developed in accordance with the above, is essentially characterized by a matrix on the basis of an acrylate-based or silicone-based non-aqueous polymer adhesive system having a solubility for the free D2-agonist base (−)-5,6,7,8-tetrahydro-6-[propyl-[2-2-thienyl)ethyl]amino]-1-naphthalenol of >5% (w/w), which matrix is substantially free of inorganic silicate particulates. The solubulity is determined at ambient temperature.

BRIEF DESCRIPTION OF THE DRAWINGS

The drawing is a plot of amount of (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol permeated versus time.

DETAILED DESCRIPTION OF THE INVENTION

In their simplest embodiment, the matrix systems are single-phase matrices. They consist of a backing layer, an active substance-containing self-adhesive matrix, and a protective film to be removed prior to use. More complicated embodiments contain multiple-layer matrices that may also contain non-adhesive layers and control membranes.

Polyacrylates are produced by radical polymerization of acrylic acid derivatives or methacrylic acid derivatives, it being quite possible to also use other suitable compounds such as, for example, vinyl acetate, as additional monomers. By selecting corresponding monomers it is possible to give each resultant adhesive specific properties.

It is common to crosslink polyacrylates with multivalent metal ions to enhance the physical properties of the adhesive or adapt it to the given requirements. Said metal ions are mostly used in the form of metal chelates which are soluble in organic solvents. Suitable compounds are, in particular, aluminum acetylacetonate or titanium acetylacetonate.

Silicone adhesives are in most cases polydimethylsiloxanes. However, other organic residues such as, for example, ethyl groups or phenyl groups may in principle be present instead of the methyl groups. Such silicone adhesives are available as one-component adhesives in two variants, as so-called amine-resistant and as non-amine-resistant adhesives. Due to the basic nature of (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol, for a silicone adhesive containing this active substance, amine-resistant adhesives are used.

Such amine-resistant silicone adhesives stand out for their not having free silanol functions. In a special process the Si—OH groups are provided with an alkyl residue. Such adhesives and their production are described in detail in EP 0 180 377.

The adhesive's dissolving capacity for the active substance is an important parameter for the development of matrix systems, just as the mobility of the active substance in the matrix, and its transfer via the contact surface to the skin, which transfer is substantially determined by corresponding distribution coefficients and the skin absorption. This results in a relatively complicated set of influences which have to be taken into account.

In systems wherein the active substance is only partially dissolved the concentration of the dissolved active substance is equal to the saturation concentration and thus has the maximum thermodynamic activity under these conditions. In general, it is, above all, the kind and quantity of the free functional groups in the adhesive which are important for the dissolving capacity of the polyacrylate adhesives. With respect to (−)-5,6,7,8-tetrahydro&[propyl-[2-(2-thienyl) ethyl]amino]-1-naphthalenol, however, it was found that the solubility of the free base is largely independent thereof, and lies in the range of between 15–35% (w/w). Such a system must therefore contain the active substance in a concentration of at least 10% (w/w) in order to come sufficiently near to the maximal thermodynamic activity. For the hydrochloride of (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl] amino]-1-naphthalenol the solubility in polyacrylates having 5–10% (w/w) is much lower, so that in such systems the active substance is preferably only partially dissolved.

Since, due to its hydrophilic properties, the hydrochloride can pass the barrier of the stratum corneum only poorly, it is necessary in this case to use lipophile, monovalent acids such as, for example, oleic acid, which, in the patch matrix, partially converts the hydrochloride into the more lipophilic oleate and which, moreover, generally acts as a permeation enhancer in the skin.

Advantageously, the acrylate-based polymer adhesive contains at least two of the following monomers: acrylic acid, acrylamide, hexylacrylate, 2-ethylhexylacrylate, hydroxyethylacrylate, octylacrylate, butylacrylate, methylacrylate, glycidylacrylate, methacrylic acid, methacrylamide, hexylmethacrylate, 2-ethylhexylmethacrylate, octylmethacrylate, methylmethacrylate, glycidylmethacrylate, vinylacetate or vinylpyrrolidone.

Silicone adhesives have a comparatively low dissolving capacity for most active substances. The saturation capacity for the base (−)-5,6,7,8-tetrahydro-6-(propyl-[2-(2-thienyl) ethyl]amino]-1-naphthalenol and the hydrochloride, respectively, is about 5% (w/w), whereas the corresponding salts are practically insoluble therein. Thus, in connection with silicone adhesives only the active substance base is suitable. If a suitable substance having an increased solubility for the active substance is admixed to the silicone adhesive, the dissolving capacity for the free base in such matrices can be raised to up to 40% (w/w) without adversely affecting the physical properties of the matrix. Suitable substances are, for example, soluble polyvinylpyrrolidone, copolymers of vinylpyrrolidone and vinylacetate, polyethyleneglycol, polypropylene glycol, glycerol or fatty acid esters of glycerol, or copolymers of ethylene and vinylacetate, polyvinylpyrrolidone having proved particularly suitable.

About 1.5–5% (w/w) of polyvinylpyrrolidone in an amine-resistant silicone adhesive increase the solubility of (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl] amino]-1naphthalenol to about 10–15% (w/w). This is sufficient to dissolve 10 mg active substance in a 20 cm^2 large patch having a coat weight of the matrix of 50 g/m^2. Since with transdermal patch systems one must always assume that only about 50% of the active substance employed will be available during the period of application, given a daily dose in the range of 1–10 mg of the active substance a plaster size of between 2 and 40 cm^2 can be expected to be sufficient to achieve therapeutic plasma levels.

The polyvinylpyrrolidone dispersed in the silicone adhesive additionally has the advantage that it decreases the so-called cold flow known from silicone adhesives. The term cold flow in this connection means that the matrix behaves like a strongly viscous fluid and thus, through flowing, tends to take up a larger area. This results in the matrix after a certain time taking up a surface which is larger than the backing layer of the patch, and in the patch tending to become agglutinated to the primary packaging material. This advantage of polyvinylpyrrolidone has already been mentioned in EP 0 524 776.

To produce the patches according to this invention, (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol or the hydrochloride is dissolved or suspended in ethanol or in another suitable organic solvent, and is then added to the adhesive solution while stirring. Where the adhesive has a suitable solvent system, the active substance can also be added to the adhesive solution directly. Additional auxiliary substances can be added either to the adhesive solution, the active substance solution or to the active substance-containing adhesive solution. An auxiliary substance which advantageously is added to the active substance solution directly is, for example, an alkaline substance which is suit able of converting the active substance hydrochloride into the free active substance base. More particularly, it is preferred to use alkali metal hydroxide such as sodium or potassium hydroxide, or an alkali metal silicate such as sodium or potassium trisilicate or sodium or potassium metasilicate as the alkaline substance. After the reaction, the solution may optionally be filtered, whereby the reactants, with the exception of the active substance base, are quantitatively practically eliminated. Said reactants are sodium chloride or potassium chloride in the case that sodium hydroxide or potassium hydroxide, respectively, are used, and sodium chloride or potassium chloride and polymeric silicon dioxide in the case that sodium or potassium silicates, respectively, are used. The resultant active substance containing adhesive solution is coated onto a suitable sheet, and the solvents are removed in a drying process. Thereafter, the backing layer of the patch is laminated onto the substantially solvent-free matrix layer, and the patches are punched out of the total laminate.

The permeation properties are advantageously enhanced by permeation enhancers which may be selected from the group of fatty alcohols, fatty acids, fatty acid esters, fatty acid amides, glycerol or its fatty acid esters, N-methylpyrrolidone, terpenes such as limonene, α-pinene, α-terpineol, carvone, carveol, limonene oxide, pinene oxide, 1,8-eucalyptol.

Details of the production and the permeation rates achieved by the finished patches will be given in the examples and the permeation studies. The polyacrylate adhesives mentioned in Examples 1–3 are to be understood

as examples and may be readily replaced by other acrylate adhesives suitable for medicinal use.

The finished plasters were used in permeation studies utilizing Franz diffusion cells and human epidermis. The results are listed in FIG. 1. It will be seen that all plasters are capable of systemically providing a sufficient amount of active substance through the skin. The present invention demonstrates that in the case of the free bases the active substance release is markedly improved as compared to the use of salts. It will also be seen that the silicone adhesive-based plasters, although having a considerably lower active substance content, deliver approximately the same quantity of active substance via the skin as the systems based on polyacrylate adhesives.

Thus, the systems according to the invention make it possible to administer the necessary daily dose of the dopamine agonist of the structure as indicated above transdermally through the skin by means of a patch having a size of approximately 20 cm^2 Since the patches can be easily manufactured, and since they deliver the active substance to the skin on their entire matrix surface, and are suitable both for the active substance salts and for the active substance bases, they constitute a considerable improvement over the known systems as described in WO 94/07468.

EXAMPLE 1

Polyacrylate System with (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol

66 g of a 50% solution of Eudragit E100 in ethyl acetate are added to 264 g of a solution of a polyacrylate adhesive having a solids content of 50%; after addition of 36 g oleyl alcohol, the mass is homogenized by stirring.

Thereafter, 89.65 g (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol are dissolved in 200 ml methylethylketone and added to the above-mentioned mass while stirring. After homogenization of the mass, it is coated onto a siliconized polyester film using a suitable doctor knife. The thickness of the moist film is adjusted such that after removal of the solvent by drying for 30 minutes at 50° C. a coat weight of 60 g/m^2 results.

The dried matrix film is then laminated with a 13 μm-thick polyester film. From the resultant patch laminate, the finished patches are punched out at the desired size, and packed in packaging material bags.

The concentration of (−)-5,6,7,8-tetrahydro-6[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol base in the patch matrix is 30.8%. Suitable polyacrylate adhesives are, for example, Durotak 387-2051, Durotak 387-2287, Durotak 387-2353, Durotal 387-2516; all of National Starch & Chemical.

The permeation rates through human epidermis under in-vitro conditions are shown in FIG. 1.

EXAMPLE 2

Silicone System with (−)-5,6,7,8-tetrahydro-6 [propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol

18 g (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl] amino]-1-naphthalenol dissolved in 40 g ethanol are added to 24 g of a 25% solution of Kollidon 90F and the mass is homogenized. Subsequently, 251 g of a solution of an amineresistant silicone adhesive having a solids content of 70% are added to this mass, and the mass is homogenized by further stirring.

Subsequently, the mass is coated, using a suitable doctor knife, onto a polyester film (Scotchpak 1022) that has been rendered adhesive, at such a thickness that after removal of the solvents by drying for 30 minutes at 50° C. a coat weight of 50 g/m^2 results.

The dried matrix film is then laminated with a 13-μm-thick polyester film. From the resultant patch laminate the finished patches are then punched out in the desired size, and packed in material bags.

The concentration of (−)-5,6,7,8-tetrahydro-6-[propyl-[2 (2-thienyl)ethyl]amino]-1-naphthalenol base in the patch matrix is 9%.

Suitable amine-resistant silicone adhesives are, for example, BIO-PSA Q7-4301 and BIO-PSA Q7-4201, both by Dow Corning.

The permeation rates through human epidermis achieved under in-vitro conditions are shown in FIG. 1.

EXAMPLE 3

Polyacrylate System with the Hydrochloride of (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl] amino]-1-naphthalenol

10 g of the hydrochloride are worked into 70 g polyacrylate adhesive (Durotak 387-2287, solids content 50%, National Starch & Chemical), and subsequently 4 g oleic acid are added. The mass is then coated onto a siliconized polyester film at such a thickness that after the removal of the solvents a coat weight of 60 g/m^2 results. The solvents are removed by drying for 15–20 minutes at a temperature between 40 and 80° C. Thereafter, the dried matrix layer is laminated with a 12–30 μm thick polyester film, and the patches are punched out.

EXAMPLE 4

20 g (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl] amino]-1-naphthalenol hydrochloride are stirred, together with 8.0 g sodium metasilicate or 9.1 g sodium trisilicate, in 35 ml ethanol for 48 hours, at room temperature.

Optionally, the active substance solution is now filtered and 6.0 g polyvinylpyrrolidone (Kollidon F90, Bayer), in the form of a 25% (w/w) solution in ethanol, and 25 g of a 70% solution of an amine-resistant silicone adhesive (Q7-4301, Dow Corning) in heptane are added and the mass is subsequently homogenized by mechanical stirring.

For manufacture of the patch matrix, the mass is subsequently coated onto a suitable film which has been rendered adhesive, and the solvents are removed by drying for 20 minutes at 50° C. The coat weight of the dried matrix film is approximately 50 g/m^2.

The dried matrix film is laminated with a 23-μm-thick polyester film. The individual patches are punched out of the complete laminate. If the active substance solution is filtered, the composition of the finished patch corresponds to that of the patch according to Example 2.

EXAMPLE 5

25 g (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl] amino]-1-naphthalenol hydrochloride are stirred, together with 14.7 g sodium metasilicate or 16.8 g sodium trisilicate, in 40 ml ethanol for 48 hours at room temperature.

Optionally, the active substance solution is now filtered and 9.2 g oleyl alcohol, 63,2 g of a 52% solution of a polyacrylate adhesive (Durotak 387-2287, National Starch & Chemical) and 22.8 g of a 40% (w/w) solution of Eudragit E100(Rohm-Pharma) are added, and the mass is subsequently homogenized by mechanical stirring.

For manufacture of the patch matrix, the mass is subsequently coated onto a suitable film which has been rendered adhesive, and the solution is removed by drying for 20

minutes at 50° C. The coat weight of the dried matrix film is approximately 80 g/m^2.

The dried matrix film is laminated with a 23-μm-thick polyester film. The individual patches are punched out of the complete laminate.

EXAMPLE 6

20 g (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl] amino]-1-naphthalenol hydrochloride are added to an ethanolic NaOH or KOH solution which contains equimolar quantities of base (2.27 g NaOH, respectively 3.19 g KOH). Preferably, the solution has a concentration of 1.5 mol/1. The conversion of the active substance salt takes place within minutes, whereby the greatest part of the NaCl formed precipitates and the active substance base dissolves completely. Optionally, a buffer solution is now added to the active substance solution in order to remove possible excess base. Likewise optionally, the active substance solution can now be filtered; 6.0 g polyvinylpyrrolidone (Kollidon F90, Bayer) in the form of a 25% solution (w/w) in ethanol and 250 g of a 70% solution of an amine-resistant silicone adhesive (Q7-4301, Dow Corning) in heptane are added, and the mass is subsequently homogenized by mechanical stirring.

For manufacture of the patch matrix, the mass is then coated onto a suitable film which has been rendered adhesive, and the solvents are removed by drying for 20 minutes at 50° C. The coat weight of the dried matrix film is approximately 50 g/m^2.

The dried matrix film is laminated with 23-μm-thick polyester film. The individual patches are punched out of the complete laminate. If the active substance solution is filtered, the composition of the finished patch corresponds to that of the patch according to Example 2.

EXAMPLE 7

Analogously to Example 6, 25 g (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol hydrocholoride are reacted with 2.84 g NaOH, respectively 3.99 g KOH, in ethanolic solution. As in Example 6, optionally a buffer is added to the active substance solution, respectively the solution is filtered, and subsequently 9.2 g oleyl alcohol, 63.2 g of a 52% solution of a polyacrylate adhesive (Durotak 387-2287, National Starch &Chemical) and 22.8 g of a 40% (w/w) solution of Eudragit E100 (Rohm-Pharma) are added, and the mass is then by mechanical stirring.

For manufacturing the patch matrix, the mass is subsequently coated onto a suitable film which has been rendered adhesive, and the solvents are removed by drying for 20 minutes at 50° C. The coat weight of the dried matrix film is approximately 80 g/m^2.

The dried matrix film is laminated with a 23-μm-thick polyester film; the individual plasters are punched out of the complete laminate.

What is claimed is:

1. A transdermal therapeutic system comprising a self-adhesive matrix layer containing the free base (−)-5,6,7,8-tetrahydro-6-[propyl-1[2-(2-thienyl)ethyl]amino]-1-naphthalenol in an amount effective for the treatment of the symptoms of Parkinson's syndrome, wherein the matrix is based on a an acrylate-based or silicone-based polymer adhesive system having a solubility of ≧5% (w/w) for the free base (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl) ethyl]-amino]-1-naphthalenol, all of said free base being present in the matrix in the absence of water; a backing layer inert to the components of the matrix layer; and a protective foil or sheet covering the matrix layer to be removed prior to use.

2. The transdermal therapeutic system of claim 1 further comprising <0.5% (w/w) inorganic silicate particulates in the matrix layer.

3. The transdermal therapeutic system of claim 1 further comprising <0.05% (w/w) inorganic silicate particulates in the matrix layer.

4. The transdermal therapeutic system of claim 1 wherein the acrylate-based polymer adhesive in the matrix layer contains at least two monomers selected from the group of acrylic acid, acrylamide, hexylacrylate, 2-ethylhexylacrylate, hydroxyethylacrylate, octylacrylate, butylacrylate, methylacrylate, glycidylacrylate, methacrylic acid, methacrylamide, hexylmethacrylate, 2-ethyhexylmethacrylate, octylmethacrylate, methylmethacrylate, glycidylmethacrylate, vinylacetate and vinylpyrrolidone.

5. The transdermal therapeutic system of claim 1 wherein the silicone-based polymer adhesive in the matrix layer further comprises additives to enhance the solubility of (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl] amino]-1-naphthalenol in the form of hydrophilic polymers or glycerol or glycerol derivatives.

6. The transdermal therapeutic system of claim 4 wherein the acrylate-based polymer contains between 10 to 40% (w/w) (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol.

7. The transdermal therapeutic system of claim 5 wherein the silicone-based polymer adhesive contains between 5 to 25% (w/w) (−)-5,6,7,8-tetrahydro[propyl-[2-(2-thienyl) ethyl]-amino]-1-naphthalenol.

8. The transdermal therapeutic system of claim 6 further comprising substances which enhance the permeation of (−)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl] amino]-1-naphthalenol into the human skin.

9. The transdermal therapeutic system of claim 7 further comprising substances which enhance the permeation of (−)-5,6,7, 8-tetrahydro-6-[propyl-[2-(2a thienyl)ethyl] amino]-1-naphthalenol into the human skin.

10. The transdermal therapeutic system of claim 8 wherein the permeation-enhancing substance is selected from the group of fatty alcohols, fatty acids, fatty acid esters, fatty acid amides, glycerol or its derivatives, N-methyl-pyrrolidone, terpenes, and terpene derivatives.

11. The transdermal therapeutic system of claim 9 wherein the permeation-enhancing substance is selected from the group of fatty alcohols, fatty acids, fatty acid esters, fatty acid amides, glycerol or its derivatives, N-methyl-pyrrolidone, terpenes, and terpene derivatives.

12. The transdermal therapeutic system of claim 10 wherein the permeation-enhancing substance is oleic acid or oleyl alcohol.

13. The transdermal therapeutic system of claim 11 wherein the permeation-enhancing substance is oleic acid or oleyl alcohol.

14. The transdermal therapeutic system of claim 5, wherein the hydrophilic polymer is selected from the group of polyvinylpyrrolidone, a copolymer of vinylpyrrolidone and vinylacetate, polyethyleneglycol, polypropylene glycol, and a copolymer of ethylene and vinylacetate.

15. The transdermal therapeutic system of claim 14 wherein the hydrophilic polymer is soluble polyvinylpyrrolidone, and wherein the soluble polyvinylpyrrolidone is present in the active substance-containing matrix layer at a concentration of between 1.5 and 5% (w/w).

16. The transdermal system of claim 1 wherein the matrix further comprises inert fillers to improve cohesion.

* * * * *

EXHIBIT H

Description and composition of the drug product

Rotigotine patch is a matrix-type transdermal system consisting of the following three main components.

(1) Flexible colored backing film (BF)

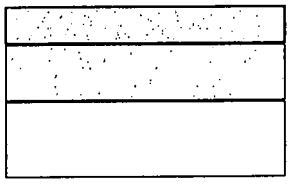
(2) Self adhesive, drug-loaded silicone matrix (DM)

(3) Protective liner (release liner, PL)

For all patch sizes the composition per area unit is identical and the patch size is identical with the drug release area.

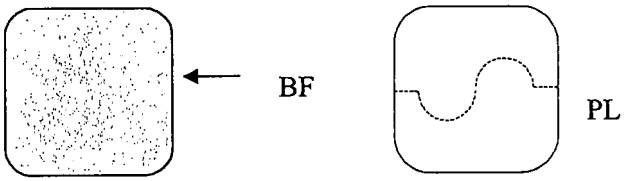
Schematic structure of rotigotine patches

Cross sectional view



Top view

Front Back



The following table describes the quantitative composition of the patches.

Composition of rotigotine patches

Material	%
Rotigotine	9.00
Povidone	2.00
Purified water	[a]

[a] removed during processing, not present in finished product

Components of the drug product

Rotigotine patch is a matrix-type transdermal system. The matrix is composed of silicone pressure-sensitive adhesives. Rotigotine and povidone, the hydrophilic matrix component are homogenously dispersed in the matrix.

EXHIBIT I

Handbook of PHARMACEUTICAL EXCIPIENTS

Third Edition

Edited by

Arthur H. Kibbe, Ph.D.
Professor and Chair
Department of Pharmaceutical Sciences
Wilkes University School of Pharmacy
Wilkes-Barre, Pennsylvania

American Pharmaceutical Association
Washington, D.C.

London, United Kingdom

Povidone

1. Nonproprietary Names

BP: Povidone
JP: Povidone
PhEur: Polyvidonum
USP: Povidone

2. Synonyms

E1201; *Kollidon*; *Plasdone*; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

3. Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4. Empirical Formula and Molecular Weight

$(C_6H_9NO)_n$ 2500-3 000 000

The USP describes povidone as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a K-value, ranging from 10-120. The K-value is calculated using Fikentscher's equation[1] shown below:

$$\log z = c\left(\frac{75k^2}{1+1.5kc}\right)+k$$

where z is the relative viscosity of the solution of concentration c, k is the K-value × 10^{-3}, and c is the concentration in % w/v.

Alternatively, the K-value may be determined from the following equation:

$$\text{K-value} = \sqrt{\frac{300\,c\log z+(c+1.5\,c\log z)^2+1.5}{0.15c+0.003c^2}}$$

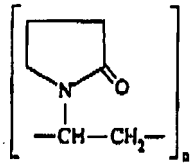
where z is the relative viscosity of the solution of concentration c, k is the K-value × 10^{-3}, and c is the concentration in % w/v.

Approximate molecular weights for different povidone grades are shown below:

K-value	Approximate molecular weight
12	2500
15	8000
17	10 000
25	30 000
30	50 000
60	400 000
90	1 000 000
120	3 000 000

See also Section 8.

5. Structural Formula



6. Functional Category

Disintegrant; dissolution aid; suspending agent; tablet binder.

7. Applications in Pharmaceutical Formulation or Technology

Although povidone is used in a variety of pharmaceutical formulations it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes.[2,3] Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a disintegrant [4,5] and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.[6-8] Povidone solutions may also be used as coating agents.

Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

Special grades of pyrogen-free povidone are available and have been used in parenteral formulations, *see* Section 14.

Use	Concentration (%)
Carrier for drugs	10-25
Dispersing agent	Up to 5
Eye drops	2-10
Suspending agent	Up to 5
Tablet binder, tablet diluent, or coating agent	0.5-5

8. Description

Povidone is a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and exist as spheres. Povidone K-90 and higher K-value povidones are manufactured by drum drying and exist as plates.

9. Pharmacopeial Specifications

Test	JP	PhEur	USP
Identification	—	+	+
Characters	+	+	—
pH	—	—	3.0-7.0
K ≤ 30	3.0-5.0	3.0-5.0	—
K > 30	4.0-7.0	4.0-7.0	—
Appearance of solution	+	+	—
Water	≤ 5.0%	≤ 5.0%	≤ 5.0%
Residue on ignition	≤ 0.1%	—	≤ 0.1%
Sulfated ash	—	≤ 0.1%	—
Lead	—	—	≤ 10 ppm

EXHIBIT J

INVESTIGATIONAL NEW DRUG APPLICATION

26 April 1995

Serial No.: 000

SPONSOR:

Discovery Therapeutics, Inc.
Richmond, VA

NAME OF DRUG:

N-0923

Volume 1 of 16

CATO
RESEARCH

200 Westpark Corporate Center
4364 South Alston Avenue
Durham, North Carolina 27713-2280
☎ 919·361·2286 Fax 919·361·2290

25 April 1995

Paul Leber, M.D.
Director, Division of Neuropharmacological
Drug Products, HFD-120
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Central Document Room
12420 Parklawn Drive, Room 214
Rockville, MD 20852

RE: Initial IND
Serial Number: 000
Discovery Therapeutics, Inc.
N-0923

Dear Dr. Leber:

On behalf of the sponsor, Discovery Therapeutics, Inc., an Investigational New Drug Application (IND) is herewith submitted. Discovery Therapeutics, Inc. intends to develop its compound N-0923 in a transdermal delivery system for the treatment of Parkinson's disease.

A signed Form FDA 1571 and a copy of a statement from Discovery Therapeutics, Inc. transferring certain sponsor obligations to Cato Research Ltd., a contract research organization, is attached.

Cato Research is responsible for maintaining this IND and submitting reports as required under 21 CFR 312. Please direct all communications regarding this IND to my attention and I will keep Discovery Therapeutics, Inc. fully informed.

If you have any questions or need additional information, please do not hesitate to call. Thank you for your consideration.

Sincerely yours,

Susan Watts

Susan Watts, Ph.D.
Regulatory Affairs Specialist

Enclosure

0001

EXHIBIT K

Received 05/18/95 sdw

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 47,852

Date MAY 12 1995

Discovery Therapeutics, Inc.
Attn: Susan L. Watts, Ph.D.
Cato Research, LTD
4364 S. Alston Avenue
Durham, North Carolina 27713

Dear Sir or Madam:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to Section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: **47,852**

Sponsor: **Discovery Therapeutics, Inc.**

Name of Drug: **N-0923**

Date of Submission: **April 26, 1995**

Date of Receipt: **April 27, 1995**

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act (Title 21 of the Code of Federal Regulations). Those responsibilities include reporting any adverse experience associated with use of the drug that is both serious and unexpected to the FDA as soon as possible and in no event later than 10 working days after initial receipt of the information and reporting any unexpected fatal or life-threatening experience to the FDA by telephone no later than 3 working days after receipt of the information (21 CFR 312.32), and submission of annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this IND, please contact Fred Abramek
Consumer Safety Officer
(301) 594-2777

Sincerely yours,

John S. Purvis

John Purvis
Supervisory Consumer Safety Officer
Division of Neuropharmacologic Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research

cc: Original IND - pink
HFD-120 - yellow
HFD-120/CSO - green

IND ACKNOWLEDGEMENT

EXHIBIT L

SCHWARZ
PHARMA

January 19, 2005

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products (HFD-120)
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

Shipping Address:
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 21-829 Neupro® (rotigotine transdermal system) (SPM 962)
For the treatment of Parkinson's disease
Original New Drug Application - Resubmission

Dear Dr. Katz:

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act, we are submitting a New Drug Application for Neupro® (rotigotine transdermal system) for the treatment of signs and symptoms of early-stage idiopathic Parkinson's disease.

Reference is made to correspondence dated November 24, 2004 in which the Division notified us that the original submission would not be filed due to inadequacies in the electronic NDA (eCTD). We have worked carefully to address each of the concerns outlined by FDA. In addition, we have conducted a careful review all components of the electronic NDA to assure that any additional deficiencies were identified and corrected. We believe that this resubmission is more consistent with FDA expectations for electronic submissions.

We are seeking approval of four sizes of the transdermal system:

Neupro Dose/24 hours	Rotigotine Content per System	Neupro System Size
2 mg	4.5 mg	10 cm^2
4 mg	9.0 mg	20 cm^2
6 mg	13.5 mg	30 cm^2
8 mg	18.0 mg	40 cm^2

SCHWARZ BIOSCIENCES, Inc.
Mail P.O. Box 110167 · Research Triangle Park · NC 27709 · Via Courier 4101 Research Commons Building · Suite 100 · 79 T.W. Alexander Drive · Research Triangle Park · NC 27709 · USA
Phone +1 919 767 2555 · Toll Free +1 866 724 2467 · Fax +1 919 767 2570 · www.schwarzpharma.com

BACKGROUND

The original IND for rotigotine (N-0923) was for an intravenous formulation that was submitted by the National Institutes of Health (NIH) on August 28, 1989 and was designated IND 33,585. Three years later, on June 25, 1992 the responsibility for this IND was transferred to Whitby Research. In a letter dated April 24, 1994, responsibility for the IND was transferred to Discovery Therapeutics. Subsequently on September 1, 1994 CATO Research Ltd. (a contract research organization) assumed administrative responsibilities for the IND.

On September 9, 1994 an IND amendment was submitted to support a transdermal dosage form. On September 29, 1994 FDA informed the Sponsor that a new IND would have to be filed for this new dosage form. The IND for the transdermal dosage form was submitted on April 25, 1995; this IND (47,852) was sponsored by Discovery Therapeutics and administered by CATO Research.

On June 15, 1995 the Sponsor requested that IND 33,585 for the intravenous formulation be placed on inactive status.

Effective October 16, 1998, sponsorship of this IND was transferred from Discovery Therapeutics to Schwarz Pharma, Inc.

CLINICAL DEVELOPMENT

In the End-of-Phase 2 meeting of June 14, 2001, FDA agreed that they would consider an application for an early-stage Parkinson's disease indication.

The development program consisted of two pivotal studies in subjects with early-stage, idiopathic Parkinson's disease. Trials SP512 (Part I) and SP513 (Part I) had similar trial designs and endpoints and meet the definition of adequate and well-controlled trials for registration. SP512 was a multicenter, double-blind, placebo-controlled, parallel group efficacy and safety study conducted in the US and Canada. SP513 was a multicenter, double-blind, double-dummy, placebo- and ropinirole-controlled, efficacy and safety study conducted in Europe, South Africa, the Middle East, Australia, and New Zealand. Both studies were designed in accordance with guidance received during the development from the FDA.

CTD ORGANIZATION

This electronic submission is formatted as a Common Technical Document (eCTD). The following modules are provided in electronic format:

Module 1: Administrative Information and Prescribing Information
Module 2: Summary
Module 3: Quality
Module 4: Safety
Module 5: Clinical Study Reports

SCHWARZ
PHARMA

We have incorporated most aspects of the Integrated Summary of Safety (ISS) into the Module 2, Clinical Summary of Safety following the ICH guidance for this section. Tables referenced in this section are hyperlinked to Module 5. Since all elements of the (ISS) are not captured by the ICH guidance for Module 2, we have included an ISS in module 5 which captures those elements that are not part of the Clinical Summary of Safety. To clarify the presentation of safety data, Module 1 folder, "Correspondence Regarding Meetings" contains a summary of presentation of safety data in response to requests from FDA. This folder also contains our list of IND's and NDA's, and a summary of correspondence with FDA over the development of rotigotine.

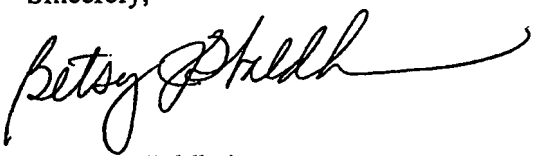
This submission is a full electronic submission. As agreed in a teleconference with FDA on August 29, 2003 and confirmed at the pre-NDA meeting on December 17, 2003, SAS Transport datasets would obviate the need for PDF format case report tabulations in the original application.

One archival copy is being submitted which contains the electronic media along with signed paper copies of the cover letter, Form FDA 356h, patent information/certification (Form FDA 3542a), debarment certification, field copy certification, financial disclosure information (signed Form FDA 3454) and a copy of the user fee cover sheet.

This submission consists of 3 DVDs and is approximately 9 gigabytes in size. All files were determined to be virus free using Symantec Antivirus Corporate Edition program version 9.0.0.338 and H+BEDV Datentechnik GmbH Anti-Vir Professional Edition V.6.29.0.8. .

We look forward to working with the Division to facilitate the approval of Neupro® for the treatment of signs and symptoms of early-stage idiopathic Parkinson's disease. If you have any questions regarding this submission, please contact me at (919) 767-2560 (phone) and (919) 767-2570 (fax) or in my absence Alan Blumberg, Ph.D., Sr. Director, Regulatory Affairs at (919) 767-3146.

Sincerely,



Betsy J. Waldheim
Head, US Regulatory Affairs
Email: betsy.waldheim@schwarzbiosciences.com

EXHIBIT M

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-829

Schwarz BioSciences, Inc.
Attention: Betsy Waldheim
Head, U.S. Regulatory Affairs
P.O. Box 110167
Research Triangle Park, NC 27709

Dear Ms. Waldheim:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act in response to our November 24, 2004 refusal to file letter for the following:

Name of Drug Product:	(rotigotine) transdermal system
Review Priority Classification:	Standard (S)
Date of Application:	January 19, 2005
Date of Receipt:	January 28, 2005
Our Reference Number:	NDA 21-829

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 29, 2005 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be **November 28, 2005.**

Under 21 CFR 314.102(c) of the new drug regulations you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. However, since this disease is not found in pediatric patients we are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submission to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products
Attention: Division Document Room, 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, call CDR Teresa Wheelous, Sr. Regulatory Project Manager, at (301)594-5504.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
3/16/05 09:16:44 AM

EXHIBIT N

IND 47,852 Chronology

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
26-Apr-95	000	Initial IND	Initial IND for Parkinson's
02-May-95		FDA Phone Contact	FDA calls requests 10 copies of Investigator's Brochure
02-May-95		Response to FDA Request for Information	Fax FDA copy of 1572 as requested
03-May-95		Response to FDA Request for Information	Send IB
12-May-95		FDA Correspondence	FDA Acknowledges receipt of IND and assigns IND number
15-May-95		FDA Phone Contact	FDA calls with Pharm/Tox reviewer questions
19-May-95	001	Response to FDA Request for Information	Submit FDA requested toxicokinetics tables and copies on Pharmacology reports cited in summary tables
25-May-95		FDA Correspondence	FDA faxes questions regarding histopathology, ADME studies and clarity of clinical information
25-May-95		FDA Phone Contact	FDA calls to state sponsor is clear to begin protocol
20-Jul-95		FDA Phone Contact	Call FDA to discuss DTI in middle of Phase I volunteer study
21-Jul-95		FDA Correspondence	FDA faxes clinical clarity concerns
04-Aug-95		Response to FDA Request for Information	Fax FDA questions on FDA concerns with clarity
19-Oct-95	002	Information Amendment: Clinical	Submit AE/EGC summaries
19-Oct-95	002	Protocol Amendment: New Protocol	
19-Oct-95	002	Protocol Amendment: New Investigator	
06-Nov-95		FDA Correspondence	FDA letter to notify clearance to begin open label phase I study only and to request additional information on clinical, pharmacology, CMC and biopharmaceutics
20-Nov-95		FDA Phone Contact	Call FDA on 20th to discuss some questions in 6-nov-95 FDA letter.

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
28-Nov-95		Other	Fax FDA questions on 6-Nov-95 FDA letter
30-Nov-95	003	Response to FDA Request for Information	
30-Nov-95	003	Information Amendment: Clinical	Revised investigator brochure
30-Nov-95	003	Protocol Amendment: Change in Protocol	Amendment 1
11-Jan-96		FDA Phone Contact	FDA calls with approval to initiate protocol 002
08-May-96	004	Protocol Amendment: Change in Protocol	Amendment 2
08-May-96	004	Information Amendment: CMC Data	Amend stability protocol
13-Aug-96	005	Annual Report	Period covering 26-apr-95 through 26-apr-96
13-Aug-96	005	Information Amendment: Clinical	Revised investigator brochure
26-Sep-96	006	Information Amendment: Clinical	
27-Sep-96	007	Information Amendment: Clinical	Revised IB
27-Sep-96	007	Information Amendment: CMC Data	New formulation at a new contract manufacturer
27-Sep-96	007	Information Amendment: Pharmacology/Toxicolo	
27-Sep-96	007	Information Amendment: Clinical	Draft protocol
27-Sep-96	007	Protocol Amendment: New Protocol	New Protocol
27-Sep-96	007	Protocol Amendment: New Investigator	
30-Sep-96		FDA Phone Contact	Call FDA to inform of Serial No. 006 and 007 submission contents
29-Oct-96		FDA Phone Contact	Call FDA to see if there are any reviewer comments regarding protocol. FDA okay to initiate protocol.
07-Nov-96	008	Protocol Amendment: New Protocol	New Protocol
07-Nov-96	008	Protocol Amendment: New Investigator	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
07-Nov-96	008	Information Amendment: Clinical	Revised IB
21-Nov-96	009	Protocol Amendment: Change in Protocol	Amendment 1
21-Nov-96	009	Protocol Amendment: New Investigator	
17-Dec-96	010	Protocol Amendment: New Investigator	
18-Dec-96	011	FDA Meeting Request	Request meeting with FDA to discuss pharm/tox program
22-Jan-97		FDA Phone Contact	FDA waiting on response from Pharm team leader for a meeting date
07-Feb-97		FDA Phone Contact	FDA calls to set up meeting date and to discuss medical reviewer involvement
12-Feb-97		FDA Phone Contact	FDA received DMF for the determination of levels in human plasma
14-Feb-97		Other	Fax FDA issues to discuss at teleconference
14-Feb-97		FDA Phone Contact	FDA calls to clarify some points in fax for discussion at teleconference
14-Feb-97	012	Information Amendment: Clinical	
18-Feb-97	013	Information Amendment: Clinical	
04-Mar-97		FDA Correspondence	FDA sends comments after review of Serial No. 007
04-Mar-97		FDA Phone Contact	FDA teleconference
15-Apr-97	014	Information Amendment: Pharmacology/Toxicolo	
15-Apr-97	014	Information Amendment: CMC Data	In response to teleconference 4-Mar-97, submit summary table of lots of DS used in nonclinical and clinical studies
12-Jun-97	015	Protocol Amendment: Change in Protocol	Amendment 1
12-Jun-97	015	Protocol Amendment: New Investigator	
16-Sep-97	016	Protocol Amendment: Change in Protocol	Amendment 2
16-Sep-97	016	General Correspondence	Letter of Authorization

Submission Date	Serial No	Submission Type	Title of Report
22-Sep-97	017	Annual Report	Period covering 26-apr-96 through 26-apr-97
06-May-98	018	Response to FDA Request for Information	Response to FDA letter 4-mar-97 regarding protocol
06-May-98	018	Information Amendment: Clinical	
06-May-98	018	Meeting Request	Request end of phase 2 meeting with FDA to discuss the design on phase 3 studies and nonclinical program
15-May-98		FDA Phone Contact	FDA calls to state that a meeting can be requested once a phase III protocol is submitted
27-Jul-98	019	Annual Report	Period covering 26-apr-97 through 26-apr-98 with revised IB
21-Oct-98	020	General Correspondence	Transfer of Ownership of IND to Schwarz Pharma, Inc.
23-Oct-98	021	General Correspondence	Notifies FDA that Schwarz Pharma, Inc. acepts all rights and responsiblities of IND 47,852
18-Feb-99		FDA Correspondence	FDA acknowledges transfer of ownership of IND
24-Feb-99	022	Information Amendment: Pharmacology/Toxicolo	
26-Feb-99	023	Information Amendment: Clinical	Revised IB
26-Feb-99	023	Protocol Amendment: New Protocol	New Protocol
26-Feb-99	023	Protocol Amendment: New Investigator	
08-Mar-99		FDA Phone Contact	Call FDA to discuss End of Phase II meeting
18-Mar-99	024	Protocol Amendment: Change in Protocol	Amendment 1
23-Mar-99	025	Protocol Amendment: New Protocol	New Protocol
23-Mar-99	025	Protocol Amendment: New Investigator	
24-Mar-99	026	Information Amendment: CMC Data	Submit CMC information to support new formulation
26-Mar-99		FDA Phone Contact	FDA,calls to discuss protocol
29-Mar-99	027	FDA Meeting Request	Request meeting and submit draft agenda

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
29-Mar-99		General Correspondence	Fax FDA revisions to protocol as discussed on 26-mar-99
01-Apr-99	028	Initial Safety Report	
13-Apr-99		FDA Phone Contact	FDA grants meeting request
23-Apr-99	029	Protocol Amendment: Change in Protocol	Amendment 1
13-May-99		FDA Phone Contact	Call FDA to discuss review of meeting package
13-May-99	030	General Correspondence	Meeting package for 26-may-99 meeting
21-May-99	031	Protocol Amendment: Change in Protocol	Amendment 2
21-May-99	031	Protocol Amendment: New Investigator	
24-May-99		FDA Phone Contact	FDA calls to request additional pharm/tox information
26-May-99		FDA Meeting	
28-May-99		FDA Phone Contact	Call FDA to discuss protocol information
10-Jun-99	032	SB Meeting Minutes	Submit meeting minutes of 26-may-99 teleconference
17-Jun-99	033	Protocol Amendment: Change in Protocol	Amendment 2
22-Jun-99		FDA Phone Contact	FDA calls to discuss amendment 2
24-Jun-99	034	Annual Report	Period covering 26-apr-98 through 25-apr-99
24-Jun-99		FDA Phone Contact	Call FDA to follow-up on request for teleconference
30-Jun-99	035	Information Amendment: CMC Data	Sample clinical supply labels
30-Jun-99	035	Protocol Amendment: New Protocol	New Protocol
30-Jun-99	035	Protocol Amendment: New Investigator	
14-Jul-99	036	Response to FDA Request for Information	Submit requested QT data

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
16-Jul-99	037	Information Amendment: CMC Data	Submit in-process controls, intermediate specifications and analytical methods for the drug substance. Also include 6 month stability data
30-Jul-99	038	Response to FDA Request for Information	Submit requested QTcf data
02-Aug-99		FDA Phone Contact	FDA calls with message about initiating amendment 2
19-Aug-99	039	Response to FDA Request for Information	Submit disk of 14-jul-99 data
02-Sep-99	040	Initial Safety Report	
10-Sep-99	041	Protocol Amendment: New Protocol	New Protocol
10-Sep-99	041	Protocol Amendment: New Investigator	
17-Sep-99	042	Follow-up Safety Report	
04-Oct-99	043	Information Amendment: Clinical	Revised IB
07-Oct-99		FDA Phone Contact	FDA calls to request 3 month toxicity reports in rats and mice
11-Oct-99	044	Information Amendment: Pharmacology/Toxicolo	
11-Oct-99	045	Protocol Amendment: Change in Protocol	Amendment 001 and 002
11-Oct-99	046	Information Amendment: Pharmacology/Toxicolo	
02-Nov-99	047	Protocol Amendment: New Investigator	Revised 1572
03-Nov-99	048	Protocol Amendment: Change in Protocol	Amendment 0003
03-Nov-99	048	Protocol Amendment: New Investigator	Revised 1572
08-Nov-99	049	Information Amendment: CMC Data	Clinical Supply Labels
11-Nov-99	050	Protocol Amendment: New Investigator	
12-Nov-99	051	Information Amendment: CMC Data	Submit updated CMC information for the DS, DP and Placebo
22-Nov-99		FDA Correspondence	Executive Carcinogensis Assessment Committee meeting minutes from 16-nov-1999 meeting.

Submission Date	Serial No	Submission Type	Title of Report
29-Nov-99		FDA Phone Contact	Call FDA to state we are incorporating CAC committee comments into the protocols
30-Nov-99		General Correspondence	Fax question regarding proposed toxicity study for FDA comment
01-Dec-99	052	General Correspondence	Submit for comments 6-month study
03-Dec-99	053	Protocol Amendment: New Investigator	
03-Dec-99	053	Protocol Amendment: Change in Protocol	Amendment 001
09-Dec-99		FDA Phone Contact	FDA calls to inquire the status of the 3-month monkey study
09-Dec-99	054	Information Amendment: Pharmacology/Toxicolo	
17-Dec-99	055	Protocol Amendment: New Investigator	
30-Dec-99	056	Protocol Amendment: Change in Protocol	Amendment 003
04-Jan-00		FDA Phone Contact	FDA medical reviewer calls to discuss the IB
05-Jan-00		FDA Correspondence	FDA faxes comments
05-Jan-00		FDA Phone Contact	FDA calls to discuss 5-jan-00 fax
07-Jan-00	057	Protocol Amendment: New Investigator	
11-Jan-00		FDA Phone Contact	FDA medical reviewer calls to discuss 3-month toxicity study data
12-Jan-00		FDA Phone Contact	Call FDA to further discuss prolactin levels
02-Feb-00	058	Information Amendment: Pharmacology/Toxicolo	
07-Feb-00		FDA Phone Contact	Call FDA for comments from reviewing pharmacologist
14-Feb-00		FDA Phone Contact	Call FDA to discuss logistics for adding foreign clinical sites
16-Feb-00	059	Protocol Amendment: New Investigator	
15-Mar-00	060	Information Amendment: Pharmacology/Toxicolo	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
20-Mar-00	061	Protocol Amendment: New Investigator	
29-Mar-00	062	Protocol Amendment: Change in Protocol	Amendment 0004 and Amendment 0005
31-Mar-00	063	Follow-up Safety Report	
05-Apr-00		FDA Correspondence	FDA sends statistical and clinical questions on 10-sep-99 submission
06-Apr-00		FDA Phone Contact	Call FDA for follow-up on pharmacologist review letter
13-Apr-00	064	Protocol Amendment: New Investigator	
18-Apr-00	065	Protocol Amendment: Change in Protocol	Amendment 002
02-May-00	066	Protocol Amendment: New Investigator	
04-May-00	067	Information Amendment: Pharmacology/Toxicolo	
12-May-00	068	Protocol Amendment: New Investigator	
01-Jun-00	069	Information Amendment: CMC Data	Submit revised CMC information
09-Jun-00		FDA Correspondence	FDA acknowledges and revises records to reflect ownership transfer to Schwarz
13-Jun-00	070	Protocol Amendment: New Investigator	
13-Jun-00		FDA Phone Contact	Call FDA to follow-up on status of reviewing pharmacologists' letter
13-Jun-00	070	Protocol Amendment: Change in Protocol	Amendment 003
14-Jun-00		FDA Phone Contact	Call FDA to discuss two adverse event reports
21-Jun-00		Response to FDA Request for Information	Submit protocol and amendments 001 and 002
22-Jun-00	071	Protocol Amendment: New Investigator	
27-Jun-00	072	Initial Safety Report	
27-Jun-00	072	Initial Safety Report	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
27-Jun-00	073	Annual Report	Period covering 26-apr-99 through 25-apr-00
30-Jun-00		FDA Phone Contact	FDA medical reviewer calls to discuss 29-mar-00 submission
30-Jun-00		FDA Phone Contact	Call FDA medical reviewer to discuss additional information
30-Jun-00	074	General Correspondence	Request final comments
12-Jul-00	075	Protocol Amendment: New Investigator	
26-Jul-00		FDA Phone Contact	FDA calls in response to written request for comment from pharmacology reviewer
26-Jul-00	076	Protocol Amendment: New Investigator	
28-Jul-00	077	General Correspondence	Request FDA comment to proposed trademark names
03-Aug-00	078	Initial Safety Report	
07-Aug-00		FDA Phone Contact	Call FDA to follow-up on requested final nonclinical comments and discuss items needed to review draft names
10-Aug-00	079	Protocol Amendment: New Investigator	
10-Aug-00	079	Protocol Amendment: New Investigator	
11-Aug-00	080	Follow-up Safety Report	
16-Aug-00		FDA Phone Contact	
21-Aug-00		FDA Phone Contact	Call FDA regarding outstanding pharmacology comments
28-Aug-00	081	Follow-up Safety Report	
31-Aug-00		FDA Phone Contact	Call FDA to discuss getting pharmacologist comments and phase IIb meeting
06-Sep-00	082	Protocol Amendment: Change in Protocol	Amendment 004
13-Sep-00		FDA Phone Contact	Call FDA; suggests we submit a meeting request.
13-Sep-00		FDA Meeting Minutes	FDA sends meeting minutes from 26-may-99

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
19-Sep-00	083	Response to FDA Request for Information	Response to 30-jun-00 teleconference issues discussed
20-Sep-00	084	Protocol Amendment: New Investigator	
29-Sep-00		FDA Correspondence	FDA sends comments to 19-sep-00 submission of response to FDA request
12-Oct-00		FDA Phone Contact	
12-Oct-00		Response to FDA Request for Information	Send safety reports previously submitted
24-Oct-00	085	Protocol Amendment: New Investigator	
24-Oct-00	085	Protocol Amendment: New Investigator	
30-Oct-00		FDA Phone Contact	FDA calls to check status of response to FDA comments 29-sep-00
02-Nov-00	086	Response to FDA Request for Information	Submit requested interval data
03-Nov-00	087	Request FDA Comment	Request comment to draft protocols
09-Nov-00	088	Initial Safety Report	
10-Nov-00	089	Response to FDA Request for Information	Respond to FDA fax 29-sep-00
17-Nov-00		FDA Phone Contact	
29-Nov-00	090	Protocol Amendment: New Investigator	
06-Dec-00		FDA Phone Contact	FDA calls back in response to questions about FDA review of 10-nov-00 submission
20-Dec-00		FDA Phone Contact	FDA medical reviewer calls to request a new protocol
05-Jan-01		FDA Phone Contact	Call FDA for status of 3-nov-00 submission of draft nonclinical protocols
10-Jan-01		FDA Correspondence	FDA letter with questions/comments
31-Jan-01		FDA Correspondence	FDA letter with comments to 3-nov-00 protocol
21-Feb-01	091	Information Amendment: Pharmacology/Toxicolo	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
23-Feb-01	092	Response to FDA Request for Information	Respond to FDA letter 10-jan-01
19-Mar-01	093	Request FDA Comment	Submit interim reports
30-Mar-01		FDA Phone Contact	FDA calls to discuss email from pharmacology reviewer regarding 19-mar-01
17-Apr-01		FDA Correspondence	FDA faxes minutes of Executive CAC meeting on 10-apr-01
20-Apr-01	094	Meeting Request	Request End of Phase II Meeting
26-Apr-01	095	Protocol Amendment: New Investigator	
04-May-01		FDA Phone Contact	FDA calls regarding meeting request for 14-jun-01
18-May-01		FDA Correspondence	FDA fax with comments
18-May-01	096	Meeting Package	Submit End of Phase II meeting package
31-May-01	097	Request FDA Comment	Submit Draft reports for FDA comment
31-May-01	098	Response to FDA Request for Information	Submit information requested for pharmacologist
05-Jun-01		FDA Correspondence	FDA faxes list of attendees
08-Jun-01		FDA Correspondence	FDA faxes questions to be discussed in end of phase II meeting
12-Jun-01		Response to FDA Request for Information	Email FDA responses to medical reviewer questions faxed 8-jun-01
14-Jun-01		FDA Meeting	End of Phase II Meeting
15-Jun-01	099	Response to FDA Request for Information	Hardcopy of information sent via email to respond to FDA questions faxed 8-jun-01
06-Jul-01	100	SB Meeting Minutes	Submit meeting minutes from 14-jun-01 end of phase II meeting
16-Jul-01		General Correspondence	Submit status report
18-Jul-01	102	General Correspondence	Notify FDA
18-Jul-01	101	Information Amendment: Pharmacology/Toxicolo	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
18-Jul-01		FDA Correspondence	FDA agrees
23-Jul-01	103	Information Amendment: Clinical	Revised IB dated 18-jun-01
27-Jul-01	104	Annual Report	Period covering 26-apr-00 through 25-apr-01
02-Aug-01		FDA Correspondence	FDA faxes pharmacology comment
06-Aug-01		FDA Correspondence	FDA letter with recommendation to dose range finding study
08-Aug-01		Annual Report	Submit one original copy of annual report 26-apr-00 through 25-apr-01
13-Aug-01		FDA Correspondence	FDA sends post-meeting comments
24-Aug-01	105	Request FDA Comment	Submit 83 week exposure data
24-Aug-01		FDA Phone Contact	Call FDA to notify of 24-aug-01 submission
04-Sep-01		FDA Correspondence	FDA faxes comments from executive CAC
05-Sep-01		FDA Meeting Minutes	FDA sends minutes from 14-jun-01 meeting with FDA
03-Oct-01	106	Information Amendment: CMC Data	Revised CMC information on DS, DP and placebo to support phase III program
03-Oct-01	106	Information Amendment: Clinical	
08-Oct-01	107	Information Amendment: Pharmacology/Toxicolo	
12-Oct-01	108	Request FDA Comment	Propose alternate analysis strategy
15-Oct-01	109	Protocol Amendment: New Protocol	Original Protocol
15-Oct-01	109	Protocol Amendment: New Investigator	
15-Oct-01	109	Information Amendment: CMC Data	Clinical Supply Labels
16-Oct-01	110	Other	Correction of Letter 15-oct-01
19-Oct-01	111	Protocol Amendment: New Protocol	Original Protocol

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
19-Oct-01	111	Protocol Amendment: New Investigator	
19-Oct-01	111	Information Amendment: CMC Data	Sample clincial supply labels
22-Oct-01	112	Request FDA Comment	Request FDA executive CAC
23-Oct-01		FDA Phone Contact	Call FDA to discuss pharmacologist review
26-Oct-01	113	General Correspondence	Send requested changes to FDA minutes of 14-jun-01 meeting
31-Oct-01		FDA Correspondence	FDA faxes recommendation from executive CAC
15-Nov-01		FDA Phone Contact	FDA calls with pharmacologist conclusion
21-Nov-01		FDA Phone Contact	FDA call to discuss our requested changes
20-Dec-01	114	Protocol Amendment: New Investigator	
20-Dec-01	114	Protocol Amendment: New Investigator	
10-Jan-02		FDA Correspondence	FDA sends fax of bullet points clarification
11-Jan-02		FDA Phone Contact	FDA calls to check receipt of 10-jan-02 fax; ask about the status of 12-oct-01 proposal; listed as ongoing
15-Jan-02		FDA Correspondence	FDA fax ok
24-Jan-02	115	Protocol Amendment: New Investigator	
24-Jan-02	115	Protocol Amendment: New Investigator	
14-Feb-02	116	Protocol Amendment: New Investigator	
14-Feb-02	116	Protocol Amendment: New Investigator	
15-Feb-02		FDA Correspondence	FDA faxes pharmacologist comment
14-Mar-02	117	Initial Safety Report	
20-Mar-02		General Correspondence	Fax FDA two follow-up questions in response to FDA 15-jan-02 fax

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
27-Mar-02	118	Protocol Amendment: New Investigator	
27-Mar-02	118	Protocol Amendment: New Investigator	
16-Apr-02	119	Protocol Amendment: New Investigator	
16-Apr-02		FDA Phone Contact	FDA calls with medical reviewer question
16-Apr-02		FDA Correspondence	FDA faxes statistical reviewer comments
16-Apr-02	119	Protocol Amendment: New Investigator	
19-Apr-02	120	Meeting Request	Meeting Request for type B meeting
07-May-02	121	Protocol Amendment: Change in Protocol	Amendment 1
07-May-02	121	Protocol Amendment: Change in Protocol	Amendment 1
07-May-02	121	Information Amendment: CMC Data	Sample clinical supply labels
14-May-02	122	Protocol Amendment: New Investigator	
14-May-02	122	Protocol Amendment: New Investigator	
15-May-02		FDA Correspondence	FDA faxes recommendations to future protocol amendment submissions.
15-May-02		FDA Phone Contact	Call FDA to respond to FDA fax 15-may-02
17-May-02	123	Meeting Package	
21-May-02	124	Information Amendment: CMC Data	Submit CMC information amendment
31-May-02		FDA Phone Contact	Call FDA to follow-up on 15-may-02 discussion
13-Jun-02	125	General Correspondence	Submit track changes versions of revised protocols
18-Jun-02	126	Initial Safety Report	
19-Jun-02		FDA Phone Contact	FDA calls for additional information

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
19-Jun-02		FDA Correspondence	FDA faxes list of attendees for 25-jun-02 meeting
20-Jun-02	127	Protocol Amendment: New Investigator	
25-Jun-02		FDA Meeting	CMC Meeting
02-Jul-02	128	Initial Safety Report	
09-Jul-02	129	Follow-up Safety Report	
09-Jul-02	130	SB Meeting Minutes	Meeting Minutes for 25-jun-02 CMC meeting with FDA
17-Jul-02	131	Protocol Amendment: New Investigator	
19-Jul-02	132	Information Amendment: Pharmacology/Toxicolo	
25-Jul-02	133	Annual Report	Period covering 26-apr-01 through 25-apr-02
01-Aug-02	134	Follow-up Safety Report	
01-Aug-02	134	Follow-up Safety Report	
05-Aug-02		7-Day Safety Report	
06-Aug-02	135	Initial Safety Report	
08-Aug-02	137	Initial Safety Report	
08-Aug-02	136	7-Day Safety Report	
08-Aug-02	137	Initial Safety Report	
13-Aug-02		FDA Meeting Minutes	FDA faxes June 25, 2002 Telecon Meeting Minutes
19-Aug-02	138	Follow-up Safety Report	
21-Aug-02	139	Initial Safety Report	
23-Aug-02	140	Protocol Amendment: New Investigator	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
05-Sep-02	141	Initial Safety Report	
11-Sep-02	142	Follow-up Safety Report	
11-Sep-02	143	General Correspondence	Submit position paper and draft report
23-Oct-02	144	Protocol Amendment: New Investigator	
31-Oct-02	145	Initial Safety Report	
12-Nov-02	146	Follow-up Safety Report	
15-Nov-02		FDA Correspondence	FDA sends fax to respond to 11-sep-02 request
19-Nov-02	147	Follow-up Safety Report	
20-Nov-02	148	Protocol Amendment: New Investigator	
19-Dec-02	150	Protocol Amendment: New Investigator	
19-Dec-02	149	General Correspondence	Schwarz submits two protocols
02-Jan-03	151	7-Day Safety Report	
22-Jan-03	152	Protocol Amendment: New Investigator	
31-Jan-03	153	General Correspondence	Submit protocol
10-Feb-03	154	Follow-up Safety Report	
13-Feb-03	155	Information Amendment: Pharmacology/Toxicolo	
19-Feb-03	156	7-Day Safety Report	
20-Feb-03	0157	Protocol Amendment: New Investigator	
03-Mar-03	0158	Information Amendment: CMC Data	Revise chemistry, manufacturing and control information and includes stability data.
11-Mar-03	0159	Initial Safety Report	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
13-Mar-03	0161	Follow-up Safety Report	
13-Mar-03		FDA Correspondence	FDA completes review of feasibility studies
20-Mar-03	0160	Protocol Amendment: New Investigator	
20-Mar-03	0161	Follow-up Safety Report	
24-Mar-03		FDA Correspondence	FDA faxes questions
25-Mar-03	0162	Follow-up Safety Report	
26-Mar-03	0163	Information Amendment: Clinical	Revised Investigator brochure dated 03-feb-2003
03-Apr-03	0164	Information Amendment: Pharmacology/Toxicolo	
10-Apr-03	0166	Follow-up Safety Report	
10-Apr-03	0165	Response to FDA Request for Information	Respond to FDA fax 24-mar-2003
11-Apr-03	0167	Initial Safety Report	
22-Apr-03	0168	Protocol Amendment: Change in Protocol	Amendment 2
22-Apr-03	0168	Protocol Amendment: New Investigator	
06-May-03	0169	Follow-up Safety Report	
07-May-03	0170	Initial Safety Report	
09-May-03	0171	7-Day Safety Report	
14-May-03	0172	7-Day Safety Report	
16-May-03	0173	Follow-up Safety Report	
20-May-03	0174	Initial Safety Report	
21-May-03	0175	Protocol Amendment: New Investigator	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
22-May-03	0176	Information Amendment: Pharmacology/Toxicolo	
28-May-03		FDA Phone Contact	FDA calls with request
28-May-03	0177	Initial Safety Report	
29-May-03	0178	Follow-up Safety Report	
29-May-03	0178	Follow-up Safety Report	
30-May-03		FDA Phone Contact	Schwarz calls FDA
05-Jun-03	0179	Protocol Amendment: Change in Protocol	Amendment 2
06-Jun-03	0180	Other	Request for special protocol assessment
06-Jun-03	0181	Follow-up Safety Report	
09-Jun-03	0183	Response to FDA Request for Information	Respond to FDA request
09-Jun-03	0182	Initial Safety Report	
09-Jun-03	0183	Follow-up Safety Report	
10-Jun-03	0184	Follow-up Safety Report	
24-Jun-03	0185	Protocol Amendment: New Investigator	
27-Jun-03	0186	Follow-up Safety Report	
30-Jun-03		FDA Correspondence	FDA requests SAS code
09-Jul-03		FDA Correspondence	FDA faxes statistical comments
16-Jul-03	0187	Initial Safety Report	
17-Jul-03	0188	Response to FDA Request for Information	Schwarz submits findings from the ECG analyses
17-Jul-03	0188	Information Amendment: Clinical	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
21-Jul-03	0189	Protocol Amendment: New Investigator	
22-Jul-03	0190	Annual Report	Period covering 26-apr-2002 through 25-apr-2003
31-Jul-03	0191	Follow-up Safety Report	
06-Aug-03	0192	General Correspondence	Request for trade name review and review by division of medication error and technical support (DMETS)
08-Aug-03		FDA Phone Contact	Call FDA to discuss potentially submitting an NDA
20-Aug-03	0193	Follow-up Safety Report	
21-Aug-03	0194	Protocol Amendment: New Investigator	
29-Aug-03	0195	General Correspondence	Respond to 18-aug-2003 FDA request
29-Aug-03		FDA Phone Contact	FDA teleconference to discuss readable CRTs in NDA
02-Sep-03	0196	7-Day Safety Report	
03-Sep-03		FDA Phone Contact	Call FDA medical reviewer with responses
04-Sep-03	0197	Response to FDA Request for Information	Respond to FDA request 29-aug-2003
11-Sep-03	0198	Follow-up Safety Report	
17-Sep-03	0199	Follow-up Safety Report	
19-Sep-03	0200	General Correspondence: Safety	
22-Sep-03	0201	Protocol Amendment: New Investigator	
01-Oct-03	0202	Response to FDA Request for Information	Submit SAS data
06-Oct-03		General Correspondence	Email FDA to confirm our understanding of the eCTD submission process
06-Oct-03		FDA Correspondence	FDA emails response to eCTD questions
10-Oct-03	0203	General Correspondence: Safety	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
14-Oct-03	0204	Follow-up Safety Report	
15-Oct-03	0205	Pre-NDA Meeting Request	Schwarz requests a type B pre-NDA meeting for the week of 15-dec-2003.
23-Oct-03	0207	Follow-up Safety Report	
23-Oct-03	0206	Initial Safety Report	
27-Oct-03	0208	Initial Safety Report	
31-Oct-03	0209	General Correspondence: Safety	
04-Nov-03	0210	Follow-up Safety Report	
06-Nov-03	0211	Follow-up Safety Report	
13-Nov-03	0212	Meeting Package	Submit Pre-NDA meeting package for 17-dec-2003 meeting.
18-Nov-03	0213	General Correspondence: Safety	
20-Nov-03	0214	Protocol Amendment: New Investigator	
24-Nov-03	0216	Initial Safety Report	
24-Nov-03	0215	Follow-up Safety Report	
02-Dec-03		FDA Correspondence	DMETS comments on the proposed tradenames
03-Dec-03	0217	Follow-up Safety Report	
05-Dec-03	0218	General Correspondence	Notify FDA of new contact person
08-Dec-03	0219	General Correspondence	Schwarz appreciates FDA comment
08-Dec-03	0220	General Correspondence	Schwarz requests additional information
12-Dec-03	0221	General Correspondence: Safety	Schwarz submits CIOMS forms
15-Dec-03		FDA Correspondence	FDA emails to request electronic copy of questions for FDA meeting 17-dec-2003.

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
17-Dec-03		FDA Meeting	
18-Dec-03		General Correspondence	Schwarz emails response with the agenda and questions section of the meeting package attached electronically.
18-Dec-03	0222	Protocol Amendment: New Investigator	
19-Dec-03	0223	Follow-up Safety Report	
22-Dec-03		FDA Correspondence	FDA emails request from carcinogenicity reviewer
07-Jan-04	0224	Follow-up Safety Report	
13-Jan-04		General Correspondence	Schwarz proposes to change the SAS data sets names in response to FDA fax 22-dec-2003
13-Jan-04		General Correspondence	FDA agrees to proposed name changes to SAS data sets.
16-Jan-04	0225	General Correspondence	Schwarz submits proposed lab variables
20-Jan-04	0226	Protocol Amendment: New Investigator	
21-Jan-04	0227	General Correspondence	Respond to FDA request for new SAS transport data set files.
28-Jan-04	0229	Follow-up Safety Report	
28-Jan-04	0228	Initial Safety Report	
29-Jan-04		FDA Correspondence	FDA faxes tables the FDA clinical reviewer stated would be provided
02-Feb-04	0230	SB Meeting Minutes	Schwarz submits pre-NDA meeting minutes from 17-dec-2003.
09-Feb-04	0231	7-Day Safety Report	Fax 7-day report
09-Feb-04	0231	7-Day Safety Report	
11-Feb-04	0232	General Correspondence	Submit proposal for the organization of the clincial trial data of an electronic submission and questions for FDA comment.
11-Feb-04	0232	Request FDA Comment	
17-Feb-04	0233	General Correspondence	Submit draft protocol

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
17-Feb-04	0234	Follow-up Safety Report	
18-Feb-04	0235	General Correspondence: Safety	
20-Feb-04	0236	Protocol Amendment: New Investigator	
24-Feb-04	0237	Initial Safety Report	
26-Feb-04	0238	Follow-up Safety Report	
01-Mar-04		FDA Correspondence	FDA fax of DMETS comments on proposed tradenames
19-Mar-04	0239	Protocol Amendment: Change in Protocol	Amendment 3
19-Mar-04	0239	Protocol Amendment: Change in Protocol	Amendment 3
24-Mar-04	0240	Protocol Amendment: Change in Protocol	Amendment 1
24-Mar-04	0240	Protocol Amendment: New Protocol	New Protocol
25-Mar-04	0241	7-Day Safety Report	Fax safety report
25-Mar-04	0241	7-Day Safety Report	
30-Mar-04		FDA Correspondence	Email received from FDA requesting analytes and normal ranges
30-Mar-04		Response to FDA Request for Information	Email FDA requested normal ranges
01-Apr-04	0242	Follow-up Safety Report	
12-Apr-04	0243	Follow-up Safety Report	
13-Apr-04	0244	General Correspondence: Safety	
14-Apr-04		FDA Correspondence	FDA faxes clinical pharmacology reviewer comments
16-Apr-04	0245	Information Amendment: CMC Data	Submit revised cmc data
19-Apr-04	0246	Protocol Amendment: New Investigator	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
22-Apr-04	0247	Protocol Amendment: New Protocol	New protocol
29-Apr-04	0249	Follow-up Safety Report	
29-Apr-04	0248	Initial Safety Report	
03-May-04	0250	Initial Safety Report	
07-May-04	0253	General Correspondence: Safety	
07-May-04	0252	General Correspondence: Safety	
07-May-04	0251	Information Amendment: Pharmacology/Toxicolo	
11-May-04		7-Day Safety Report	Fax FDA 7-day safety report
11-May-04	0254	7-Day Safety Report	
17-May-04	0255	General Correspondence: Safety	
17-May-04	0257	Follow-up Safety Report	
17-May-04	0256	General Correspondence: Safety	
18-May-04	0258	Initial Safety Report	
20-May-04	0259	Protocol Amendment: New Investigator	
02-Jun-04	0260	7-Day Safety Report	
02-Jun-04		7-Day Safety Report	Fax 7-day safety report
08-Jun-04	0261	Follow-up Safety Report	
09-Jun-04	0262	7-Day Safety Report	
09-Jun-04	0263	General Correspondence: Safety	
09-Jun-04	0264	General Correspondence: Safety	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
09-Jun-04	0262	7-Day Safety Report	Fax 7-day safety report
14-Jun-04	0265	General Correspondence: Safety	
16-Jun-04	0267	Follow-up Safety Report	
16-Jun-04	0266	Initial Safety Report	
22-Jun-04	0268	Protocol Amendment: New Investigator	
22-Jun-04	0269	Annual Report	Period covering 26-apr-2003 through 8-mar-2004
22-Jun-04	0268	Protocol Amendment: New Investigator	
23-Jun-04		FDA Correspondence	FDA sends fax
23-Jun-04	0271	General Correspondence	Schwarz request FDA reconsideration of proposed tradename
23-Jun-04	0270	Follow-up Safety Report	
24-Jun-04		Response to FDA Request for Information	Respond to FDA fax on 23-JUN-2004
25-Jun-04		FDA Correspondence	FDA emails
28-Jun-04	0272	General Correspondence: Safety	
30-Jun-04	0273	7-Day Safety Report	Fax 7-day safety report to FDA
30-Jun-04	0273	7-Day Safety Report	
14-Jul-04	0274	General Correspondence: Safety	
14-Jul-04	0275	Follow-up Safety Report	
19-Jul-04		FDA Phone Contact	FDA calls with DMETS response
20-Jul-04	0276	Protocol Amendment: New Investigator	
29-Jul-04	0277	General Correspondence	Request FDA review of potential tradenames

Submission Date	Serial No	Submission Type	Title of Report
04-Aug-04		FDA Correspondence	FDA responds with DMETS comments
13-Aug-04		FDA Meeting Minutes	FDA emails the pre-NDA meeting minutes from 17-DEC-2003.
16-Aug-04	0278	Follow-up Safety Report	
19-Aug-04	0279	Protocol Amendment: New Investigator	
20-Aug-04	0280	General Correspondence	Withdraw request to review trade names
23-Aug-04	0281	General Correspondence: Safety	
23-Aug-04	0282	Meeting Request	Schwarz requests type A teleconference
24-Aug-04	0283	Follow-up Safety Report	
30-Aug-04	0284	General Correspondence: Safety	
30-Aug-04	0285	General Correspondence: Safety	
31-Aug-04		General Correspondence	Email FDA that Schwarz declines teleconference date.
01-Sep-04	0286	7-Day Safety Report	
01-Sep-04		7-Day Safety Report Fax	
07-Sep-04	0287	Initial Safety Report	
08-Sep-04		General Correspondence	Fax FDA Schwarz copy of pre-NDA meeting minutes.
16-Sep-04	0288	General Correspondence: Safety	
16-Sep-04	0288	General Correspondence: Safety	
16-Sep-04	0289	General Correspondence: Safety	
16-Sep-04	0290	Follow-up Safety Report	
17-Sep-04	0291	Protocol Amendment: New Investigator	

Submission Date	Serial No	Submission Type	Title of Report
24-Sep-04	0293	General Correspondence: Safety	
24-Sep-04	0292	7-Day Safety Report	
24-Sep-04		7-Day Safety Report	Fax 7-day safety report
28-Sep-04	0294	Follow-up Safety Report	
29-Sep-04	0295	Initial Safety Report	
30-Sep-04	0296	General Correspondence: Safety	
08-Oct-04		7-Day Safety Report	Fax 7-day safety report
08-Oct-04	0297	7-Day Safety Report	
08-Oct-04	0298	Initial Safety Report	
13-Oct-04	0299	Follow-up Safety Report	
20-Oct-04	0300	Protocol Amendment: New Investigator	
22-Oct-04	0301	Follow-up Safety Report	
04-Nov-04	0302	Follow-up Safety Report	
08-Nov-04	0303	General Correspondence	Schwarz notifies FDA of central IRB address change
09-Nov-04	0304	General Correspondence: Safety	
09-Nov-04	0304	General Correspondence: Safety	
12-Nov-04	0305	Follow-up Safety Report	
19-Nov-04	0307	7-Day Safety Report	
19-Nov-04		7-Day Safety Report	Fax 7-day safety report
19-Nov-04	0306	Protocol Amendment: New Investigator	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
23-Nov-04	0308	Initial Safety Report	
30-Nov-04	0309	Protocol Amendment: New Protocol	
30-Nov-04		Response to FDA Request for Information	Email lab ranges
06-Dec-04	0310	Follow-up Safety Report	
09-Dec-04	0311	General Correspondence: Safety	
09-Dec-04	0312	Follow-up Safety Report	
20-Dec-04	0313	Protocol Amendment: New Investigator	
21-Dec-04	0314	Follow-up Safety Report	
22-Dec-04	0315	7-Day Safety Report	
22-Dec-04		7-Day Safety Report	Fax 7-day safety report
04-Jan-05	0316	Information Amendment: CMC Data	
04-Jan-05	0317	Protocol Amendment: Change in Protocol	Amendment 1
04-Jan-05	0317	Transfer of Obligations	
05-Jan-05	0318	Follow-up Safety Report	
05-Jan-05	0319	Initial Safety Report	
06-Jan-05	0320	7-Day Safety Report	
06-Jan-05		7-Day Safety Report	Fax 7-day safety report
17-Jan-05	0321	Follow-up Safety Report	
24-Jan-05	0322	Protocol Amendment: New Investigator	
27-Jan-05	0323	Follow-up Safety Report	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
01-Feb-05	0324	General Correspondence: Safety	Follow-up
03-Feb-05	0325	General Correspondence: Safety	Initial
04-Feb-05	0326	Follow-up Safety Report	
09-Feb-05	0327	Initial Safety Report	
11-Feb-05	0328	Follow-up Safety Report	
16-Feb-05	0329	General Correspondence: Safety	initial
17-Feb-05		7-Day Safety Report	Fax 7-day safety report
17-Feb-05	0330	Protocol Amendment: New Investigator	
17-Feb-05	0331	7-Day Safety Report	
18-Feb-05	0332	Initial Safety Report	
24-Feb-05	0334	Follow-up Safety Report	
24-Feb-05	0333	General Correspondence: Safety	
03-Mar-05	0335	Information Amendment: Clinical	revised investigator's brochure dated October 2004
07-Mar-05	0336	General Correspondence: Safety	
08-Mar-05	0337	7-Day Safety Report	
14-Mar-05	0338	Follow-up Safety Report	
17-Mar-05	0339	Protocol Amendment: New Investigator	
17-Mar-05	0340	Initial Safety Report	
24-Mar-05	0342	General Correspondence: Safety	
24-Mar-05	0341	Initial Safety Report	

Submission Date	Serial No	Submission Type	Title of Report
29-Mar-05	0343	Follow-up Safety Report	
29-Mar-05	0344	Initial Safety Report	
05-Apr-05	0345	Follow-up Safety Report	
12-Apr-05	0346	General Correspondence: Safety	
18-Apr-05	0349	Protocol Amendment: New Investigator	
18-Apr-05	0348	Initial Safety Report	
18-Apr-05	0347	General Correspondence: Safety	follow-up
22-Apr-05	0350	7-Day Safety Report	
22-Apr-05		7-Day Safety Report	Fax 7-day safety report
25-Apr-05	0351	General Correspondence: Safety	follow-up
27-Apr-05	0352	General Correspondence: Safety	initial
27-Apr-05	0353	7-Day Safety Report	
28-Apr-05	0354	Follow-up Safety Report	
03-May-05	0355	General Correspondence	In response to end of phase 2 meeting, Schwarz submits protocol plan
04-May-05		General Correspondence	Email FDA that the protocol plan has been submitted
05-May-05	0356	General Correspondence: Safety	follow-up
11-May-05	0357	Follow-up Safety Report	
12-May-05	0359	7-Day Safety Report	
12-May-05	0358	Initial Safety Report	
13-May-05	0360	General Correspondence: Safety	follow-up

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
13-May-05	0361	Follow-up Safety Report	
18-May-05	0362	Information Amendment: CMC Data	Submit revised CMC information
19-May-05	0363	Protocol Amendment: New Investigator	
23-May-05	0364	Follow-up Safety Report	
25-May-05	0365	General Correspondence: Safety	initial
26-May-05	0366	Initial Safety Report	
02-Jun-05	0367	Follow-up Safety Report	
06-Jun-05	0368	Follow-up Safety Report	
08-Jun-05	0369	7-Day Safety Report	
09-Jun-05	0370	Annual Report	Period covering 9-MAR-2004 through 8-MAR-2005
10-Jun-05	0371	Request FDA Comment	Submit draft protocol
14-Jun-05	0372	Follow-up Safety Report	
14-Jun-05	0373	General Correspondence: Safety	
15-Jun-05	0374	General Correspondence: Safety	initial
17-Jun-05	0375	Information Amendment: Clinical	revised investigator's brochure addendum 1 dated 7-JUN-2005
23-Jun-05	0376	Initial Safety Report	
24-Jun-05	0377	Follow-up Safety Report	
27-Jun-05	0378	Protocol Amendment: New Investigator	
28-Jun-05	0379	General Correspondence: Safety	
29-Jun-05	0380	Initial Safety Report	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
06-Jul-05	0381	Initial Safety Report	
12-Jul-05	0382	Follow-up Safety Report	
14-Jul-05	0383	Follow-up Safety Report	
20-Jul-05	0384	Protocol Amendment: New Investigator	
25-Jul-05	0385	Meeting Request	Request meeting with FDA
26-Jul-05	0386	Initial Safety Report	
28-Jul-05		FDA Correspondence	FDA email response that she is awaiting clinical pharmacology review
01-Aug-05	0387	Initial Safety Report	
03-Aug-05	0388	Follow-up Safety Report	
08-Aug-05		FDA Correspondence	FDA sets type A meeting
09-Aug-05	0389	Follow-up Safety Report	
09-Aug-05		General Correspondence	Email FDA meeting date of 9-SEP-2005 is acceptable
10-Aug-05		FDA Correspondence	FDA emails receipt of questions for meeting
12-Aug-05	0390	Initial Safety Report	
17-Aug-05	0391	Follow-up Safety Report	
17-Aug-05	0392	Meeting Package	Resend meeting package for 9-SEP-2005 meeting
19-Aug-05	0393	Protocol Amendment: New Investigator	
19-Aug-05	0393	Protocol Amendment: New Investigator	
19-Aug-05	0394	Follow-up Safety Report	
19-Aug-05	0395	General Correspondence: Safety	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
29-Aug-05	0397	Initial Safety Report	
29-Aug-05	0396	Follow-up Safety Report	
30-Aug-05		FDA Phone Contact	FDA calls requesting information
02-Sep-05		Response to FDA Request for Information	Schwarz emails FDA data and articles
07-Sep-05	0398	General Correspondence: Safety	
08-Sep-05		Response to FDA Request for Information	Schwarz emails FDA inclusion criteria amendment
08-Sep-05	0399	Initial Safety Report	
09-Sep-05		FDA Meeting	
19-Sep-05		FDA Correspondence	FDA emails statistical questions
20-Sep-05	0400	Protocol Amendment: New Investigator	
21-Sep-05	0401	Initial Safety Report	
27-Sep-05	0402	SB Meeting Minutes	Schwarz submits minutes from Type A meeting held 09-SEP-2005
28-Sep-05	0403	Initial Safety Report	
28-Sep-05	0404	General Correspondence: Safety	
29-Sep-05	0405	Follow-up Safety Report	
06-Oct-05	0406	General Correspondence	Submit response to questions from FDA
06-Oct-05		Response to FDA Request for Information	Schwarz emails FDA response
07-Oct-05	0407	Initial Safety Report	
07-Oct-05	0408	Follow-up Safety Report	
10-Oct-05	0409	Follow-up Safety Report	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
19-Oct-05	0410	Initial Safety Report	
19-Oct-05	0411	Follow-up Safety Report	
20-Oct-05	0413	Follow-up Safety Report	
20-Oct-05	0412	Protocol Amendment: New Investigator	
27-Oct-05	0414	Follow-up Safety Report	
01-Nov-05	0415	Initial Safety Report	
03-Nov-05	0416	Follow-up Safety Report	
04-Nov-05		General Correspondence	Email FDA about the Division's preference for the presentation of safety data from Phase 3 trials
07-Nov-05		FDA Correspondence	FDA emails recommendation
10-Nov-05	0417	General Correspondence	Notify FDA of change in address and fax number
16-Nov-05	0418	Initial Safety Report	
17-Nov-05	0419	General Correspondence: Safety	
18-Nov-05	0420	Follow-up Safety Report	
18-Nov-05	0421	Protocol Amendment: New Investigator	
22-Nov-05	0423	7-Day Safety Report	
22-Nov-05	0422	General Correspondence: Safety	
28-Nov-05	0424	Information Amendment: Clinical	Submit revised Investigator's Brochure dated 02-NOV-2005
29-Nov-05	0425	Follow-up Safety Report	
01-Dec-05	0426	Initial Safety Report	
06-Dec-05	0427	Follow-up Safety Report	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
06-Dec-05		FDA Correspondence	FDA acknowledges receipt of change in corporate address
09-Dec-05	0428	Follow-up Safety Report	
13-Dec-05	0429	Protocol Amendment: New Protocol	Amendment 1
16-Dec-05	0430	Initial Safety Report	
19-Dec-05	0431	General Correspondence: Safety	
21-Dec-05	0432	Follow-up Safety Report	
21-Dec-05	0433	Protocol Amendment: New Investigator	
27-Dec-05	0434	Follow-up Safety Report	
28-Dec-05	0435	Initial Safety Report	
28-Dec-05	0435	Initial Safety Report	
29-Dec-05	0436	Follow-up Safety Report	
09-Jan-06		General Correspondence	Email FDA Word version
17-Jan-06	0437	General Correspondence: Safety	
18-Jan-06	0438	General Correspondence: Safety	
19-Jan-06	0439	Follow-up Safety Report	
20-Jan-06		FDA Correspondence	FDA emails request 6-FEB-2006 teleconference at 10 am
20-Jan-06		General Correspondence	Email FDA confirmation of 6-FEB-2006 teleconference at 10 am
20-Jan-06	0440	Protocol Amendment: New Investigator	
23-Jan-06	0441	Initial Safety Report	
27-Jan-06	0442	General Correspondence: Safety	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
02-Feb-06		General Correspondence	Email FDA request for comments
06-Feb-06	0444	Follow-up Safety Report	
06-Feb-06	0443	General Correspondence: Safety	
06-Feb-06		FDA Teleconference	
09-Feb-06	0445	General Correspondence: Safety	
15-Feb-06	0446	Initial Safety Report	
21-Feb-06	0447	Protocol Amendment: New Investigator	
22-Feb-06	0450	Follow-up Safety Report	
22-Feb-06	0449	Initial Safety Report	
22-Feb-06	0448	7-Day Safety Report	
27-Feb-06		General Correspondence	Email FDA to ask about status of data analysis and data presentation comments
28-Feb-06	0451	General Correspondence: Safety	
28-Feb-06		FDA Correspondence	FDA emails that comments referenced in the 06-FEB-2006 teleconference will be sent soon after internal review
02-Mar-06		FDA Correspondence	FDA emails that comments are concerned with data analysis
06-Mar-06	0453	Follow-up Safety Report	
06-Mar-06		7-Day Safety Report Fax	
06-Mar-06	0452	7-Day Safety Report	
14-Mar-06	0456	Information Amendment: Pharmacology/Toxicolo	
14-Mar-06	0454	Initial Safety Report	
14-Mar-06	0455	Follow-up Safety Report	

Submission Date	Serial No	Submission Type	Title of Report
14-Mar-06		FDA Correspondence	FDA emails inquiry about timing of protocol submission
16-Mar-06	0457	Follow-up Safety Report	
17-Mar-06	0458	Protocol Amendment: Change in Protocol	Amendment 2
20-Mar-06	0459	Protocol Amendment: New Investigator	
22-Mar-06	0461	Follow-up Safety Report	
22-Mar-06	0460	General Correspondence: Safety	
27-Mar-06	0462	7-Day Safety Report	
29-Mar-06	0465	Protocol Amendment: Change in Protocol	Amendment 1
29-Mar-06	0464	Follow-up Safety Report	
29-Mar-06	0463	General Correspondence: Safety	
03-Apr-06	0467	General Correspondence: Safety	
03-Apr-06	0466	Follow-up Safety Report	
07-Apr-06	0468	Follow-up Safety Report	
10-Apr-06		General Correspondence	Email FDA for comment on Schwarz plan to conduct a proof of concept study
11-Apr-06	0469	7-Day Safety Report	
11-Apr-06		FDA Correspondence	FDA emails that medical reviewer would like to see a draft protocol
12-Apr-06	0470	Request FDA Comment	Request FDA comment on Schwarz proposal to conduct a proof of concept study
19-Apr-06	0471	Initial Safety Report	
19-Apr-06	0472	Follow-up Safety Report	
20-Apr-06	0473	Protocol Amendment: New Investigator	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
26-Apr-06	0474	General Correspondence: Safety	
03-May-06	0475	Initial Safety Report	
15-May-06	0477	Follow-up Safety Report	
15-May-06	0476	Initial Safety Report	
19-May-06	0478	Protocol Amendment: New Investigator	
22-May-06	0479	Protocol Amendment: Change in Protocol	Amendment 3
30-May-06	0480	Follow-up Safety Report	
05-Jun-06	0481	Annual Report	Annual report for period covering March 9, 2005 through March 8, 2006
09-Jun-06	0482	Information Amendment: Clinical	Submit revised Investigator Brochure dated 2-JUN-2006
12-Jun-06	0483	Follow-up Safety Report	
15-Jun-06	0484	Initial Safety Report	
16-Jun-06	0485	Protocol Amendment: Change in Protocol	Amendment 4
20-Jun-06	0487	Initial Safety Report	
20-Jun-06	0486	Protocol Amendment: New Investigator	
20-Jun-06	0488	General Correspondence: Safety	
29-Jun-06	0489	Follow-up Safety Report	
29-Jun-06	0490	General Correspondence: Safety	
30-Jun-06	0491	Initial Safety Report	
07-Jul-06	0492	Follow-up Safety Report	
07-Jul-06	0493	General Correspondence: Safety	

Submission Date	Serial No	Submission Type	Title of Report
11-Jul-06	0494	Information Amendment: Clinical	
13-Jul-06	0495	Initial Safety Report	
13-Jul-06	0496	Follow-up Safety Report	
20-Jul-06	0497	Protocol Amendment: New Investigator	
26-Jul-06	0498	General Correspondence	Submit proof of concept protocol
01-Aug-06	0500	General Correspondence: Safety	
01-Aug-06	0501	Follow-up Safety Report	
01-Aug-06	0502	Protocol Amendment: Change in Protocol	Amendment 4
01-Aug-06	0499	General Correspondence: Safety	
21-Aug-06	0503	Initial Safety Report	
21-Aug-06	0504	Protocol Amendment: New Investigator	
23-Aug-06		FDA Correspondence	
30-Aug-06	0505	Initial Safety Report	
30-Aug-06	0506	General Correspondence: Safety	
06-Sep-06	0507	General Correspondence: Safety	
06-Sep-06	0508	General Correspondence: Safety	
12-Sep-06	0510	Response to FDA Request for Information	Submit case report form
12-Sep-06	0511	Information Amendment: Pharmacology/Toxicolo	
12-Sep-06	0509	General Correspondence: Safety	
13-Sep-06	0512	Follow-up Safety Report	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
14-Sep-06	0513	Meeting Request	Submit Type B Pre-NDA meeting request
18-Sep-06	0514	Initial Safety Report	
18-Sep-06	0515	General Correspondence: Safety	
20-Sep-06	0516	Protocol Amendment: New Investigator	
27-Sep-06	0517	General Correspondence: Safety	
28-Sep-06	0518	Follow-up Safety Report	
29-Sep-06		FDA Correspondence	FDA emails to grant type B meeting 09-NOV-2006 from 8:30 to 10:00 am
06-Oct-06	0519	Meeting Package	Submit meeting package for 09-NOV-2006 Pre-NDA meeting
10-Oct-06	0520	General Correspondence: Safety	
10-Oct-06	0521	Follow-up Safety Report	
12-Oct-06		General Correspondence	Email FDA TOC of the tables by title
18-Oct-06	0523	Follow-up Safety Report	
20-Oct-06	0524	Protocol Amendment: New Investigator	
25-Oct-06	0525	General Correspondence	Submit financial disclosure information
27-Oct-06	0527	Follow-up Safety Report	
27-Oct-06	0526	Initial Safety Report	
01-Nov-06	0528	General Correspondence: Safety	
01-Nov-06		FDA Correspondence	FDA mails letter suggesting improvements
02-Nov-06		FDA Correspondence	FDA emails in response to 25-OCT-2006 submission
02-Nov-06		General Correspondence	Email FDA response to request for information

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
06-Nov-06	0530	General Correspondence: Safety	
06-Nov-06	0529	Initial Safety Report	
06-Nov-06		FDA Correspondence	FDA emails request for information
07-Nov-06		General Correspondence	Email FDA, TEAE and SAE tables
07-Nov-06		FDA Correspondence	FDA emails pre-meeting responses for 09-NOV-2006 Pre-NDA meeting
09-Nov-06	0531	General Correspondence: Safety	
09-Nov-06		FDA Meeting	
13-Nov-06		FDA Correspondence	FDA emails request for additional analyses
15-Nov-06	0532	Follow-up Safety Report	
16-Nov-06	0533	Request FDA Comment	Request FDA review and comment
17-Nov-06	0534	Initial Safety Report	
20-Nov-06	0535	Protocol Amendment: New Investigator	
20-Nov-06	0535	Protocol Amendment: New Investigator	
27-Nov-06	0538	General Correspondence: Safety	
27-Nov-06	0536	Initial Safety Report	
27-Nov-06	0537	Follow-up Safety Report	
28-Nov-06	0539	Follow-up Safety Report	
30-Nov-06	0540	General Correspondence: Safety	
06-Dec-06	0541	Initial Safety Report	
06-Dec-06	0542	Follow-up Safety Report	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
07-Dec-06	0543	Information Amendment: Clinical	
12-Dec-06	0544	General Correspondence: Safety	
19-Dec-06	0545	Protocol Amendment: New Investigator	
20-Dec-06	0546	Initial Safety Report	
21-Dec-06		FDA Meeting Minutes	FDA emails meeting minutes from 09-NOV-2006 pre-NDA meeting
02-Jan-07	0548	Follow-up Safety Report	
02-Jan-07	0549	General Correspondence: Safety	
04-Jan-07	0550	General Correspondence	Submit narrative criteria for review and comment
12-Jan-07	0551	General Correspondence: Safety	
19-Jan-07	0552	Protocol Amendment: New Investigator	
13-Feb-07	0553	Initial Safety Report	
13-Feb-07	0554	General Correspondence: Safety	
15-Feb-07	0555	Information Amendment: Clinical	
15-Feb-07	0556	General Correspondence	Submit mock shells of AE analyses for review and comment
16-Feb-07	0557	7-Day Safety Report	
20-Feb-07	0558	Protocol Amendment: New Investigator	
20-Feb-07	0558	Protocol Amendment: New Investigator	
22-Feb-07	0560	Follow-up Safety Report	
22-Feb-07	0559	General Correspondence: Safety	
28-Feb-07	0561	Initial Safety Report	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
28-Feb-07	0562	General Correspondence: Safety	
01-Mar-07	0563	Protocol Amendment: New Protocol	New protocol
01-Mar-07	0564	General Correspondence	Request IRB waiver
07-Mar-07	0565	Initial Safety Report	
09-Mar-07	0566	Initial Safety Report	
13-Mar-07	0567	Information Amendment: Pharmacology/Toxicolo	
14-Mar-07	0568	Protocol Amendment: Change in Protocol	Amendment 2
14-Mar-07	0568	Protocol Amendment: Change in Protocol	Amendment 3
20-Mar-07	0569	General Correspondence	Requested safety follow-up information
20-Mar-07	0570	Protocol Amendment: New Investigator	
20-Mar-07		General Correspondence	Email FDA narrative criteria
21-Mar-07	0571	Follow-up Safety Report	
21-Mar-07	0572	Information Amendment: Pharmacology/Toxicolo	
26-Mar-07	0573	General Correspondence: Safety	
03-Apr-07	0574	General Correspondence: Safety	
03-Apr-07	0575	Initial Safety Report	
04-Apr-07	0576	Protocol Amendment: Change in Protocol	Amendment 5
04-Apr-07	0576	Protocol Amendment: Change in Protocol	Amendment 5
09-Apr-07	0577	General Correspondence	send updated contact information to the IND
17-Apr-07	0578	General Correspondence: Safety	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
17-Apr-07	0579	Initial Safety Report	
19-Apr-07	0580	7-Day Safety Report	
19-Apr-07	0581	Initial Safety Report	
20-Apr-07	0582	Protocol Amendment: New Investigator	
24-Apr-07	0583	Protocol Amendment: Change in Protocol	Amendment 1
24-Apr-07	0583	Protocol Amendment: Change in Protocol	Amendment 2
26-Apr-07	0584	Protocol Amendment: Change in Protocol	Amendment 2
26-Apr-07	0585	Information Amendment: Pharmacology/Toxicolo	
27-Apr-07	0587	Follow-up Safety Report	
27-Apr-07	0586	Initial Safety Report	
30-Apr-07	0588	General Correspondence: Safety	Correction
04-May-07	0589	Initial Safety Report	
08-May-07	0590	Initial Safety Report	
16-May-07	0593	General Correspondence: Safety	
16-May-07	0591	Initial Safety Report	
16-May-07	0592	Follow-up Safety Report	
18-May-07	0594	Protocol Amendment: New Investigator	
18-May-07	0594	Protocol Amendment: New Investigator	
22-May-07	0595	General Correspondence	Notification of site closure
29-May-07	0596	Initial Safety Report	

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
29-May-07	0597	Information Amendment: Pharmacology/Toxicolo	
30-May-07	0598	Initial Safety Report	
05-Jun-07	0600	Initial Safety Report	
05-Jun-07	0602	General Correspondence: Safety	
05-Jun-07	0601	Follow-up Safety Report	
05-Jun-07	0599	7-Day Safety Report	
11-Jun-07	0603	Annual Report	Period covering March 9, 2006 through March 8, 2007
12-Jun-07	0605	Protocol Amendment: New Protocol	Postmarketing Study Commitment Protocol
13-Jun-07	0604	Initial Safety Report	
20-Jun-07	0609	Follow-up Safety Report	
20-Jun-07	0606	General Correspondence: Safety	Correction
20-Jun-07	0607	General Correspondence: Safety	
20-Jun-07	0608	General Correspondence: Safety	
20-Jun-07	0611	Protocol Amendment: New Investigator	
20-Jun-07	0610	Protocol Amendment: New Protocol	
26-Jun-07	0612	Information Amendment: Clinical	
03-Jul-07	0614	Follow-up Safety Report	
03-Jul-07	0613	Initial Safety Report	

NDA 21-829 Chronology

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
23-Mar-04		Other	Submit sample eCTD for review.
01-Apr-04		FDA Phone Contact	Call FDA to discuss feedback received regarding the sample eCTD submitted 23-mar-2004.
24-Sep-04		Original New Drug Application	Submit NDA for neupro for the treatment of the signs and symptoms of early-stage idiopathic parkinson's disease
03-Nov-04		Other	Schwarz paid the October 2004 user fee rate; however, the application was received in september. Schwarz requests refund of the difference.
23-Nov-04		Response to FDA Request for Informatio	Schwarz sends FDA requested information reagarding drug substance and drug product manufacturers
24-Nov-04		FDA Correspondence	FDA refuses to file eCTD
29-Nov-04		Meeting Request	Request type A meeting with FDA to discuss refusal to file issues.
01-Dec-04		General Correspondence	Email FDA
02-Dec-04		FDA Correspondence	FDA emails
05-Dec-04		General Correspondence	Schwarz account of meeting with FDA
13-Dec-04		General Correspondence	Schwarz emails list of attendees and questions for teleconference on 20-DEC-2004.
14-Dec-04		FDA Correspondence	FDA emails threshold requests for abnormal lab values and requests text description of these results.
03-Jan-05		General Correspondence	Schwarz emails FDA confirmation of lab thresholds request was received however without the outlier ranges attached
06-Jan-05		General Correspondence	Email FDA to discuss resubmission
19-Jan-05		Resubmission of Original New Drug Appli	Resubmission of Original New Drug Application delivered on 28-JAN-2005
18-Feb-05		Response to FDA Request for Informatio	Schwarz emails FDA location of orthostatic hypotension info

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
22-Feb-05		FDA Correspondence	FDA emails requests for identification of ISS tables
24-Feb-05		Response to FDA Request for Informatio	Email FDA map to vital sign tables and ISS tables
16-Mar-05		FDA Correspondence	FDA acknowledges receipt of NDA
24-Mar-05		FDA Phone Contact	FDA requests additional information
29-Mar-05		Response to FDA Request for Informatio	Email FDA subject and AE information
29-Mar-05		FDA Correspondence	FDA emails that the NDA is adequate for filing and comments will be sent in the 74 day letter
20-Apr-05		General Correspondence	Email FDA for status of 74-day review letter.
20-Apr-05		FDA Correspondence	FDA emails that the application is fileable and ther are no requests at this time.
26-Apr-05		FDA Correspondence	FDA Field Investigations announces GMP inspection
27-Apr-05		General Correspondence	Schwarz emails FDA to confirm GMP inspection dates.
29-Apr-05		Response to FDA Request for Informatio	Provide FDA requested information on CD for investigators audits.
06-May-05		Response to FDA Request for Informatio	Email FDA that inspection dates are acceptable
10-May-05		Response to FDA Request for Informatio	Email FDA answers to CMC questions
11-May-05		FDA Correspondence	FDA emails more CMC questions
25-May-05	0001	120-day safety update	
26-May-05		FDA Correspondence	FDA sends requests/comments for drug substance stability data
02-Jun-05		FDA Correspondence	FDA email request for safety database search of any fibrotic or potentially fibrotic complication Aes in our rotigotine trials
07-Jun-05		Response to FDA Request for Informatio	Resubmit additional CD copies of the investigator information originally submitted on 29-APR-2005
08-Jun-05		FDA Correspondence	FDA requests information on fibrosis and fibrotic complications
15-Jun-05		FDA Correspondence	FDA faxes the statistical request for ANCOVA results sent earlier via email

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
15-Jun-05		General Correspondence	Email FDA we have received the request for ANCOVA results and will be submitting a response with this information and fibrosis and CMC responses
23-Jun-05	0002	Response to FDA Request for Informatio	Response to requests: clinical, statistical, and CMC
23-Jun-05		Response to FDA Request for Informatio	Response to FDA CMC questions
13-Jul-05		FDA Phone Contact	FDA calls to request all datasets for all studies in NDA.
20-Jul-05		FDA Correspondence	FDA requests WORD version of labeling without line numbers
20-Jul-05		Response to FDA Request for Informatio	Email FDA requested package insert
29-Jul-05	0003	Response to FDA Request for Informatio	Amendment to pending application to provide the requested datasets for clinical studies
09-Aug-05	0004	Amendment to Pending Application	Submit amendment 0004 with CMC validation batch test results
10-Aug-05		FDA Correspondence	FDA requests Schwarz track data on melanoma cases in association with Parkinson's disease and submit datasets as required
18-Aug-05		General Correspondence	Email FDA location of requested datasets and SAS files previously filed in submission 0002
18-Aug-05		FDA Phone Contact	FDA calls to request datasets and SAS files previously filed in submission 0002
18-Aug-05		FDA Phone Contact	FDA calls to request datasets and SAS files previously filed in submission 0002
18-Aug-05		General Correspondence	Email FDA location of requested datasets and SAS files previously filed in submission 0002
25-Aug-05		FDA Correspondence	FDA emails request for SAScodes for tables
26-Aug-05		FDA Phone Contact	FDA calls to inform Schwarz of information requests from the safety reviewer
26-Aug-05		FDA Correspondence	FDA emails request for additional AE information
30-Aug-05		FDA Phone Contact	FDA calls to inform Schwarz of additional information requests from the safety reviewer
30-Aug-05		FDA Correspondence	FDA faxes questions from safety reviewer
01-Sep-05		FDA Correspondence	FDA emails question regarding location of narratives for all adverse events leading to discontinuation and requests clarification of inconsistency in data tables

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
01-Sep-05		Response to FDA Request for Informatio	Schwarz emails FDA to confirm receipt of emails containing safety review questions
01-Sep-05		FDA Correspondence	FDA emails questions regarding QT study
02-Sep-05		Response to FDA Request for Informatio	Schwarz emails FDA proposal for conditions of which adverse event narratives to provide
02-Sep-05		Response to FDA Request for Informatio	Schwarz emails Mr. Siddiqui, FDA, that the requested SAScodes and safety review responses will be submitted today
02-Sep-05	0005	Response to FDA Request for Informatio	Schwarz submits requested SAScodes for SP506 and answers to safety review questions
06-Sep-05		General Correspondence	Schwarz emails Mr. Nighswander, FDA, tentative list of participants in 07-SEP-2005 teleconference
06-Sep-05		FDA Correspondence	FDA acknowledges receipt of submission sequence 0005 (FDA stamp)
07-Sep-05		FDA Phone Contact	Schwarz holds teleconference with FDA to discuss proposal to submit narratives for Aes
09-Sep-05	0006	Response to FDA Request for Informatio	Schwarz submits responses to questions from safety reviewer
13-Sep-05	0007	Response to FDA Request for Informatio	Schwarz provides narratives
13-Sep-05	0005	Response to FDA Request for Informatio	Schwarz resubmits submission sequence 0005
13-Sep-05		FDA Correspondence	FDA acknowledges receipt of submission sequence 0007 (FDA stamp)
15-Sep-05		General Correspondence	CDER confirms receipt of lifecycle submission 0007
19-Sep-05		Response to FDA Request for Informatio	Schwarz emails receipt of information requests
19-Sep-05		FDA Correspondence	FDA emails information requests from safety reviewer
23-Sep-05	0008	Response to FDA Request for Informatio	Schwarz submits response to requests
26-Sep-05		FDA Phone Contact	FDA CMC drug product related questions
29-Sep-05	0009	Response to FDA Request for Informatio	Schwarz submits responses to CMC drug product questions and process validation report
03-Oct-05		FDA Correspondence	FDA acknowledges receipt of 13-SEP-2005 response to safety review questions and extends user fee goal date by three months to 28-FEB-2006
05-Oct-05	0010	Response to FDA Request for Informatio	Submit datasets fwith dosing and titration information as requested

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
31-Oct-05	0011	Response to FDA Request for Informatio	Submit datasets requested
06-Dec-05		FDA Correspondence	FDA emails request from safety reviewer
15-Dec-05	0013	Response to FDA Request for Informatio	Submit response
20-Dec-05		FDA Correspondence	FDA emails safety information requested
21-Dec-05	0014	Response to FDA Request for Informatio	Submit response to FDA containing safety information
28-Dec-05		FDA Correspondence	FDA calls to request CMC information
05-Jan-06	0015	Response to FDA Request for Informatio	Submit CMC information
17-Jan-06		FDA Correspondence	FDA emails request for information
18-Jan-06		General Correspondence	Email FDA that additional analyses would be necessary to answer safety data request
23-Jan-06		General Correspondence	Email FDA
23-Jan-06		FDA Correspondence	FDA emails request from safety reviewer
26-Jan-06	0016	Response to FDA Request for Informatio	Submit safety data
30-Jan-06	0017	Other	Amendment to Pending Application
09-Feb-06		General Correspondence	Email FDA response to preclinical question
17-Feb-06		General Correspondence	Email FDA response to CMC question
17-Feb-06		FDA Correspondence	FDA emails CMC question
23-Feb-06	0018	Response to FDA Request for Informatio	Submit Amendment to Pending Application
28-Feb-06		FDA Correspondence	FDA sends approvable letter for NDA
02-Mar-06		General Correspondence	Submit Response to Action Letter
16-Mar-06		Meeting Request	Request Type A meeting/teleconference to discuss the 28-FEB-2006 action letter

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
13-Apr-06		FDA Teleconference	Teleconference to discuss Approvable Letter
24-Apr-06		General Correspondence	Submit non-clinical response
31-May-06		SB Meeting Minutes	Submit minutes from 13-APR-2006 teleconference to discuss Approvable Letter
05-Jun-06		FDA Meeting Minutes	FDA emails meeting minutes from 13-APR-2006 teleconference
25-Aug-06	0019	Amendment to a Pending Application	Submit Amendment to Pending Application: Complete Response to Action Letter
31-Aug-06	0020	Amendment to a Pending Application	Submit draft labeling
08-Sep-06		FDA Correspondence	FDA emails clinical pharmacology information request
08-Sep-06		General Correspondence	Email response to 08-SEP-2006 clinical pharmacology information request
24-Sep-06		FDA Correspondence	FDA mails incomplete response letter
29-Sep-06		FDA Correspondence	FDA emails that safety team agrees with our interpretation
02-Oct-06	0021	Amendment to a Pending Application	Respond to FDA letter and resubmit a complete response to the action letter
16-Oct-06		FDA Correspondence	FDA mails letter to acknowledge receipt of 28-AUG-2006 submission
24-Oct-06		General Correspondence	Email FDA that Schwarz would like the clincial safety reviewer to participate in requested teleconference
24-Oct-06		General Correspondence	Email FDA to confirm teleconference on 02-NOV-2006 at 9:30 am
07-Nov-06	0022	Amendment to a Pending Application	Submit revised data set in resubmission of complete response
21-Nov-06		FDA Correspondence	FDA emails that the resubmission for NDA 21-829 is accepted as a complete response
04-Dec-06		FDA Correspondence	FDA emails request from safety reviewer
07-Dec-06	0023	Amendment to a Pending Application	Submit request
20-Dec-06		FDA Correspondence	FDA emails request for additional analyses
21-Dec-06		FDA Correspondence	FDA mails confirmation of complete response to action letter

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
05-Jan-07		FDA Correspondence	FDA emails five safety information requests
10-Jan-07	0024	Amendment to a Pending Application	Submit response to safety dataset information request
24-Jan-07	0025	Amendment to a Pending Application	Response to request for analyses
05-Feb-07	0026	Amendment to a Pending Application	Submit stability update: drug substance and drug product
02-Apr-07		FDA Correspondence	FDA letter
02-Apr-07		FDA Correspondence	
04-Apr-07	0027	Amendment to a Pending Application	CMC response to information request
18-Apr-07		FDA Correspondence	FDA emails question
23-Apr-07		General Correspondence	Email FDA revised Patient Information leaflet and tracked changes
27-Apr-07		FDA Correspondence	FDA emails request for labeling teleconference
30-Apr-07		FDA Correspondence	FDA emails DMETS labeling comments
30-Apr-07		FDA Correspondence	FDA emails draft labeling and request change in teleconference
02-May-07		General Correspondence	Email FDA packaging for Neupro inclusive of DMETS comments
02-May-07		FDA Teleconference	Labeling teleconference
02-May-07		FDA Correspondence	FDA requests recent version of labeling
04-May-07		FDA Teleconference	Labeling teleconference
04-May-07	0028	Amendment to a Pending Application	Draft Labeling
04-May-07	0029	Amendment to a Pending Application	Phase IV Commitments
04-May-07		General Correspondence	Phase 4 commitments
06-May-07		FDA Teleconference	Labeling teleconference

Submission Date	*Serial No*	*Submission Type*	*Title of Report*
08-May-07	0030	Amendment to a Pending Application	Revised Phase IV commitments
08-May-07		FDA Teleconference	Labeling teleconference
08-May-07	0031	Amendment to a Pending Application	Adhesion Specification Revision
09-May-07		FDA Correspondence	FDA mails Neupro Approval Letter
09-May-07		FDA Correspondence	Ms. Wheelous emails labeling
09-May-07		FDA Correspondence	Ms. Wheelous again emails labeling
09-May-07		General Correspondence	Email Ms. Wheelous that labeling revisions are acceptable
09-May-07		Promotional	Submit to Division Print Press Release sent to DDMAC

EXHIBIT O

CALCULATION OF LENGTH OF PATENT TERM EXTENSION FOR A HUMAN DRUG PRODUCT		
1. Enter the number of days for the testing phase as defined in 37 CFR 1.775(c)(1)		2379
2. Enter the number of days for the approval phase as defined in 37 CFR 1.775(c)(2)		841
3. Add line 1 and line 2 and enter the total here	3220	
4. Enter the number of days of the period of line 2 which occurred prior to the issue date of the patent		97
5. Enter the number of days the period of line 2 during which the applicant failed to act with due diligence as defined in 37 CFR 1.775(d)(1)(ii)		0
6. Add line 4 and line 5 and enter the total here	97	
7. Subtract line 6 from line 3 and enter the difference here (if less than zero enter 0)	3123	
8. Enter the number of days of the period of line 1 which occurred prior to the issue date of the patent		2379
9. Enter the number of days of the period of line 1 during which the applicant failed to act with due diligence as defined in 37 CFR 1.775(d)(1)(ii)		0
10. Add line 8 and line 9 and enter the total here	2379	
11. Subtract line 10 from line 7 and enter the difference here	744	
12. Enter the number of days from line 1		2379
13. Enter the number of days from line 10		2379
14. Subtract line 13 from line 12 and enter the difference here (if less than zero enter 0)		0
15. Multiply line 14 by 0.5 (one half) and enter the amount here	0	
16. Subtract line 15 from line 11 and enter the difference here (if less than zero enter 0)	744	
17. Enter the original expiration date of the patent		03.18.19
18. Enter the expiration date of the patent if extended by the number of days on line 16		03.31.21
19. Enter the date of the FDA (Food and Drug Administration) final approval		05.09.07
20. Limitation set forth in 37 CFR 1.775(d)(3)		14 Years
21. Add the number of years on line 20 to the date on line 19 and enter the revised date here		05.09.21
22. Enter the earlier date appearing on line 18 or line 21	03.31.21	
23. Enter the original expiration date of the patent (from line 17)		03.18.19
24. Check one of the following three boxes and enter the listed time period		5 Years
The patent issued after 24/9/84 — 5 Years	X	
The patent issued prior to 24/9/84 and no request for exemption as defined in 37 CFR 1.775(d)(6)(i) was filed prior to 24/9/84 — 5 Years		
The patent issued prior to 24/9/84 and an exemption as defined in 37 CFR 1.775(d)(6)(ii) was filed prior to 24/9/84 — 2 Years		
25. Add the number of years on line 24 to the date on line 23 and enter the revised date here		03.18.24
26. Enter the earlier date appearing on line 22 or line 25	03.31.21	
27. Enter the original expiration date of the patent (from line 17)	03.18.19	
28. Enter the number of days by which line 26 and line 27 differ here This is the length of patent term extension	744	

INFORMATION OBTAINED FROM THE U.S. PATENT AND TRADEMARK OFFICE